AUGUST, 1959 VOL. 78, NO. 2

American 24 Journal

# OBSTETRICS AND GYNECOLOGY

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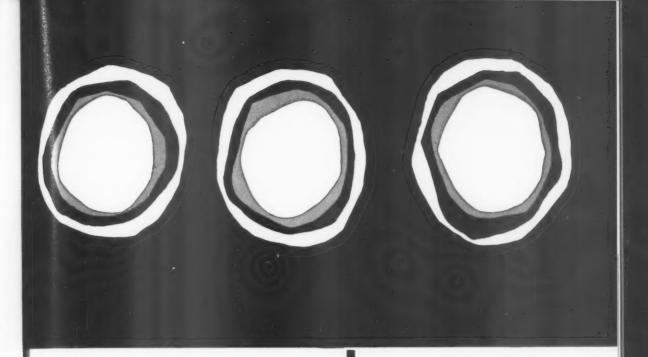
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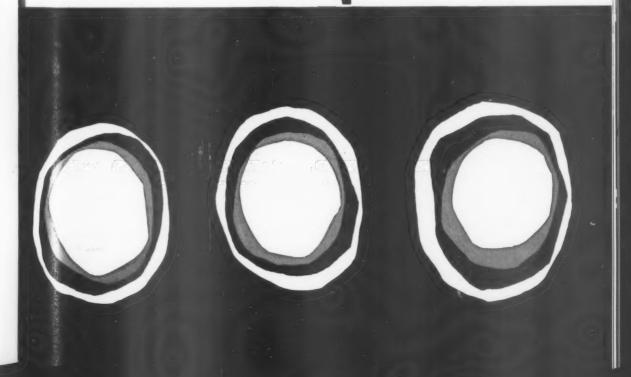
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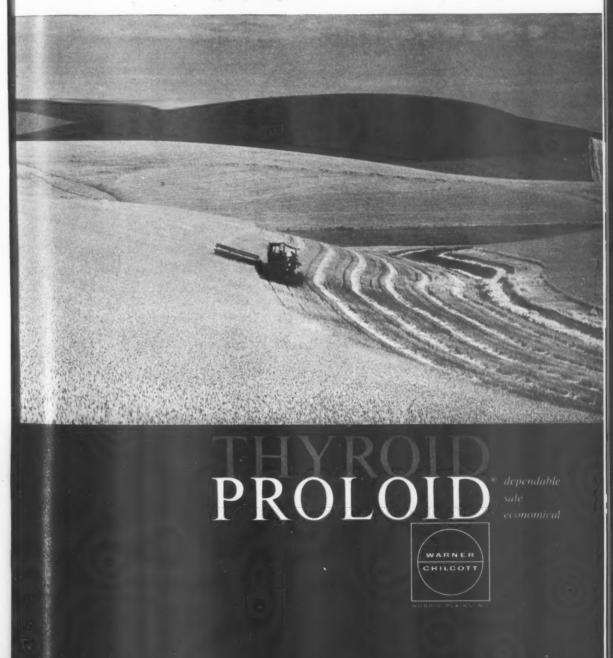
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- Council on Drugs: New and Nonofficial Drugs 1958.
   Methallenestril, Philadelphia, J. B. Lippincott Company, 1958, pp. 477-478.
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- 3. Napp, E. E.; Goldfarb, A. F., and Massell, G.: The Parenteral Use of Methallenestril for the Suppression of Lactation. A New Approach, West. J. Surg. 64:492 (Sept.) 1956.

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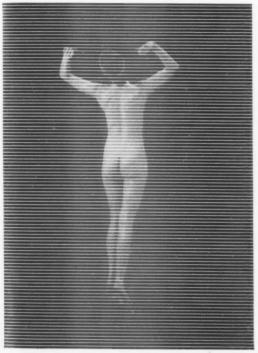
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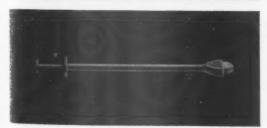
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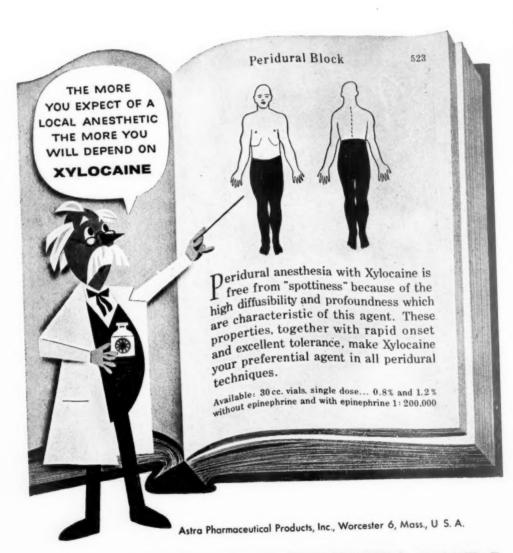
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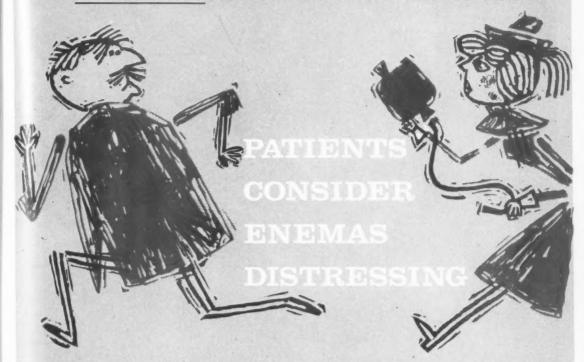
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2. Bergquist, J. R.: Personal Communication, 1957. 3. Pummer, L. R.: Personal Communication, 1957.

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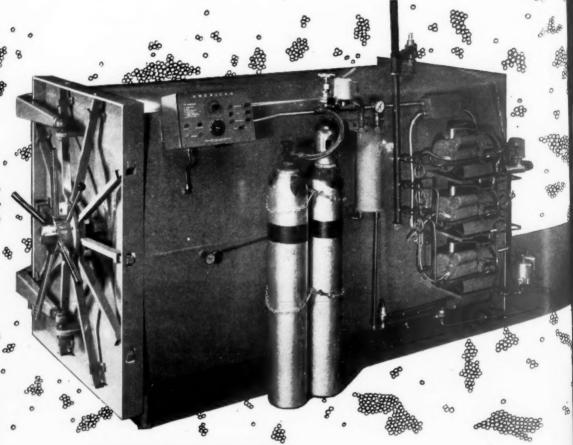
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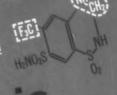
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Specially packed for spinal anesthesia in 2 cc. color break ampules; Xylocaine HCI 5% with glucose 7.5%, a sterile hyperbaric solution sp.g. 1.030-1.035.



ASTRA PHARMACEUTICAL PRODUCTS, INC., WORCESTER 6, MASS., U.S.A.

**XYLOCA** 

NE® HCI 5% WITH GLUCOSE 7.5%

\*U.S. PAT. NO. 2,441,498 MADE IN U.S.A.



in inflammatory anorectal disorders . . .

### The Promise of Greater Relief

the first suppository to contain

hydrocortisone for effective control of proctitis

- Proctitis accompanying ulcerative colitis
- Radiation proctitis
- Postoperative scar tissue with inflammatory reaction
- Acute and chronic nonspecific proctitis
- Acute internal hemorrhoids
- Medication proctitis
- Cryptitis



**Ulcerative Colitis** 



**Radiation Proctitis** 



**Postoperative** Scar Tissue

Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth



Philadelphia 1. Pà.

### dual usefulness of



# DESITIN hemorrhoidal

SUPPOSITORIES

with cod liver oil

for

hemorrhoids

in

pregnancy



a suppository, such as **Desitin**, reduces straining at the stool by lubricating the anal canal.<sup>1</sup>



conservative treatment is indicated<sup>1-3</sup> for mild to moderate symptoms of simple hemorrhoids, fissures, cryptitis, pruritus ani...in pregnant and other patients.

DESITIN SUPPOSITORIES lubricate, soothe, protect, ease pain, itching...and aid healing (with Norwegian cod liver oil, rich in vitamins A and D and unsaturated fatty acids). Free from drugs which might mask serious rectal disease.

Write for samples and literature1-3

**DESITIN** CHEMICAL COMPANY

812 Branch Ave., Providence 4, R. I.



clear,

viscous, water-soluble

1

Available in three sizes... and the single use tube for true maintenance of sterile technique.

# Lycinate TM

### PENETRATES THROUGH THE MUCO-PURULENT BARRIER



seeks out...exposes...then destroys the trichomonad

The success of leukorrhea therapy depends upon bringing effective trichomonacidal medication into contact with the exudate-protected pathogens.

Lycinate, through extremely effective mucolytic action, penetrates, exposes and then destroys these organisms by both chemotherapeutic and lysing actions.

#### EACH LYCINATE VAGINAL TABLET CONTAINS:

Diiodohydroxyquin . . . 100 mg.

Sodium lauryl sulfate . . . 5 mg.
Lactose . . . . . . . 380 mg.

Dioctyl sodium sulfosuccinate 5 mg.
Aluminum potassium sulfate 14 mg.
Dextrose, anhydrous . . . . 650 mg.

DOSAGE: 2 vaginal tablets inserted simultaneously once daily. SUPPLIED: Boxes of 50 with applicator.

LLOYD BROTHERS, INC.

CINCINNATI 3, OHIO



With Cervilaxin, the 1st stage remaining after 3.5 cm. cervical dilatation was found to be 43% to 51% shorter than with oxytocin alone...¹

"A number of our colleagues have insisted that (oxytocin) drip alone is adequate to produce these results. Our experience has convinced them that with the combined use of (oxytocin) and Cervilaxin, the remainder of the first stage, beyond an average of about 3.5 cm. dilatation is 43% to 51% less than with (oxytocin) alone."

CERVILAXIN® the highly purified, standardized preparation of relaxin—"third hormone of pregnancy"2—is indeed "a worthwhile adjunct to the medical induction of labor . . . "3

Given by intravenous drip, alone or with oxytocin, early in spontaneous or induced labor at term, CERVILAXIN acts physiologically and safely. It (1) softens the cervix, (2) eases delivery, by softening cervical and perineal tissues, and (3) avoids birth injuries, by diminishing cervical and perineal resistance to the expulsive forces of labor. In fact it makes the use of oxytocin safer as well as more efficient.

CERVILAXIN is supplied in 2-ml. vials containing 20 mg./ml., with detailed instructions for administration by intravenous drip.

References: 1. Rothman, E., Bentley, W.G., and Floyd, W.S.: Am. J. Obst. & Gynec. 78:38, 1959. 2. Stone, M.L., Sedlis, A., and Zuckerman, M.: ibid. 76:544, 1958. 3. Sands, R.X.: Canad. M.A.J. 78:935, 1958.

Products of Original Research



THE NATIONAL DRUG COMPANY

Philadelphia 44, Pa.

CE-930/59



Eradicate Infection and Restore Normal Vaginal Flora...

# New-Neosporin Vaginal Suppositories

 $Trichomonacidal \cdot Bactericidal$ 



BURROUGHS WELLCOME & CO. (U.S.A.) NC., Tuckahoe, New York

THE BUILDERED

ACID VAGINAL DOUCHE

BUFFERED

TO

AN ACID pH



Mildly astringent soothing inflamed tissue

Low surface tension effectively penetrating vaginal folds

"Clean" refreshing odor assuring patient acceptance

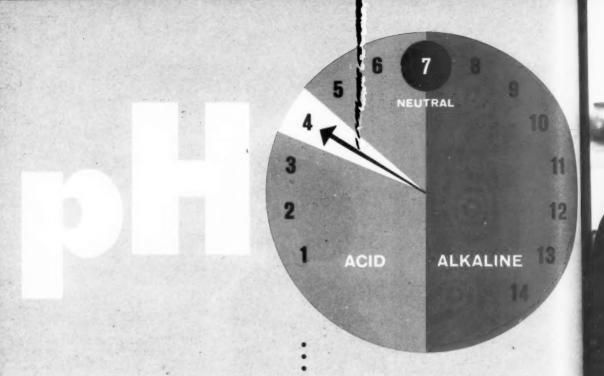
Valuable adjunct in management of monilia, trichomonas, staphylococcus and streptococcus vaginal infections.

See reverse side for detail.

MASSENGILL POWDER

THE S E MASSENGILL COMPANY

Bristol, Tennesses - New York Kames City Can Francisco



## massengill° powder

The **BUFFERED** acid vaginal douche

### What is a BUFFER?

Medical dictionaries define it as a substance which, added to a solution, causes resistance to any change of hydrogen-ion concentration (pH) when either acid or alkali is added.

THE

PR

### Significance of buffers in Massengill Powder

The normal vagina has a pH of 3 to 4.5. This low pH inhibits growth of most pathogenic invaders. Usually, an infection will cause the pH to rise to the neutral or alkaline range which favors the multiplication of pathogens.

The alkaline mucosa neutralizes a simple, unbuffered acid douche, like vinegar, within 30 minutes.

In contrast, the *buffered* acid douche solution of Massengill Powder (pH 3.5-4.5) resists neutralizing. The normal, low pH is maintained for 4 to 6 hours and as long as 24 hours in recumbent patients. This low pH inhibits the propagation of monilia, trichomonas vaginalis and pathogenic bacteria. However, the beneficial Döderlein bacillus thrives in this pH range.

### THE S. E. ASSENGILL COMPANY

Bristol, Tennessee \* New York \* Kansas City \* San Francisco



but she needs your help in planning her family

# Delfen

Preceptin<sup>®</sup>

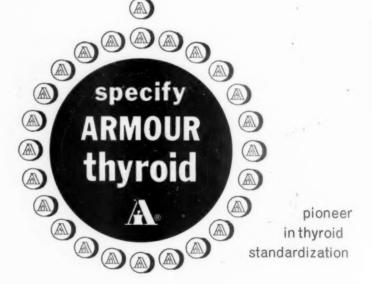
THE MODERN CHEMICAL SPERMICIDE

THE SPERMICIDAL GEL WITH BUILT-IN BARRIER

PRESCRIBED WITH CONFIDENCE FOR SIMPLE, EFFECTIVE CONTRACEPTION



for consistent therapeutic response

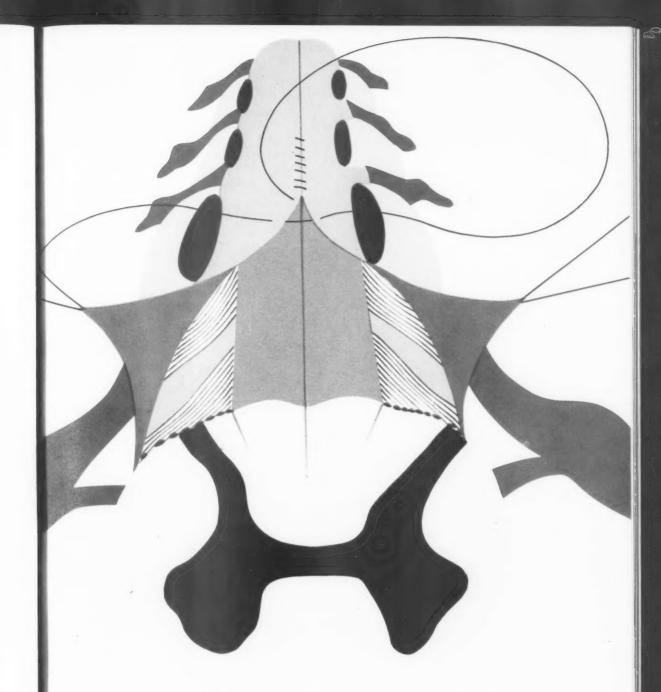


In all conditions requiring substitution therapy with thyroid hormone

Supplied in 1/4, 1/2, 1, 2 and 5 grain strengths.

ARMOUR PHARMACEUTICAL COMPANY . KANKAKEE, ILLINOI

A Leader in Biochemical Research



setting new standards

# ETHICON®

sutures

### ATRALOC\*

seamless needles less bending,

less breaking
less tissue trauma

ETHICON®

### faster recovery, greater comfort for your OB-GYN patients



Administered before and after cervicovaginal surgery, irradiation, delivery, and office procedures such as cauterization, Furacin cream promptly controls infection; reduces discharge, irritation and malodor; hastens healing. Furacin cream is active in the presence of exudates, yet is nontoxic to regenerating tissue, does not induce significant bacterial resistance nor encourage monilial overgrowth.

### FURACIN' CREAM

FURACIN 0.2% in a fine cream base, water-miscible and self-emulsifying in body fluids. Tubes of 3 oz., with plastic plunger-type vaginal applicator. Also available: FURACIN Vaginal Suppositories.



ıma

THE NITROFURANS —a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

# BONA



# DOXIN® (tablets and drops)

STOPS STOPS MORNING SICKNESS



OE RIG

New York 17, N. Y.

Division, Chas. Pfizer & Co., Inc.

Science for the World's Well-Being

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# KONAKION

Rapid action

Wide margin of safety

Versatility of administration

Compatibility

Low dosage forms

rate of absorption faster than menadione or derivatives... more potent and lasting effects.

substantially safer than vitamin-K analogues – no kernic erus reported.

capsules for oral use...fine aqueous dispersion for parenteral administration.

unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.

no excess, no waste-packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

KONAKION®-brand of vitamin . K1

ROCHE® Capsules - 5 mg; Ampuls - 1 mg/0.5 cc; 10 mg/1 cc; 25 mg/2.5 cc



ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey



In a recent placebo-controlled study of 112 patients complaining of nausea and vomiting of pregnancy, Moessner<sup>1</sup> reports 94 per cent relief of symptoms with Prozine. Optimum dosage was low, side-effects notably infrequent and mild.

PROZINE not only exerts a potent action upon the vomiting mechanism itself, but also controls apprehension and agitation as well as motor excitability by acting on both the hypothalamic and thalamic areas of the brain. PROZINE offers effective therapy in purely psychic conditions and in psychic conditions resulting from, or contributing to, organic disease.

1. Moessner, G.F.: To be Published, Western J. Surg.

#### Gravida I, Nausea and Vomiting 0





Affects the thalamic and hypothalamic areas of the brain

### PROZINE

meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL THROUGH DUAL ACTION



Philadelphia 1, Pa.

\*Trademark

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#### NOW

...a new way
to relieve pain
and stiffness
in muscles
and joints

INDICATED IN:

MUSCLE STIFFNESS

LUMBOSACRAL STRAIN

SACROILIAC STRAIN

WHIPLASH INJURY

BURSITIS

SPRAINS

TENOSYNOVITIS

FIBROSITIS

FIBROMYOSITIS

LOW BACK PAIN

DISC SYNDROME

SPRAINED BACK

"TIGHT NECK"

TRAUMATIC STRAINS

POSTOPERATIVE

- Exhibits unusual analgesic properties, different from those
- of any other drug Specific and superior in relief of SOMAtic pain
- Modifies central perception of pain without abolishing natural
- Relaxes abnormal tension of skeletal muscle defense reflexes



N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

- More specific than salicylates Less drastic than steroids
- More effective than muscle relaxants.

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. Soma is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with Soma than with any previously used analgesic, sedative or relaxant drug.

SOMA also relaxes muscle hypertonia, with its stresses on related joints. ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets. Literature and samples on request.



WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

#### **CONGESTIVE FAILURE**

"Chlorothiazide appears to represent a significant advance in the treatment of patients with congestive heart failure . . . ; its decided advantages are (1) effective oral administration, (2) apparent lack of toxicity, (3) high patient acceptance, (4) sustained diuretic action . . ."

Keyes, J.W. and Berlacher, F.J.: J.A.M.A. 169:109, (Jan. 10) 1959.

Desage: One or two 500 mg. tablets DIURIL once or twice a day.

## DI UR GRIOTOTHAZIDE

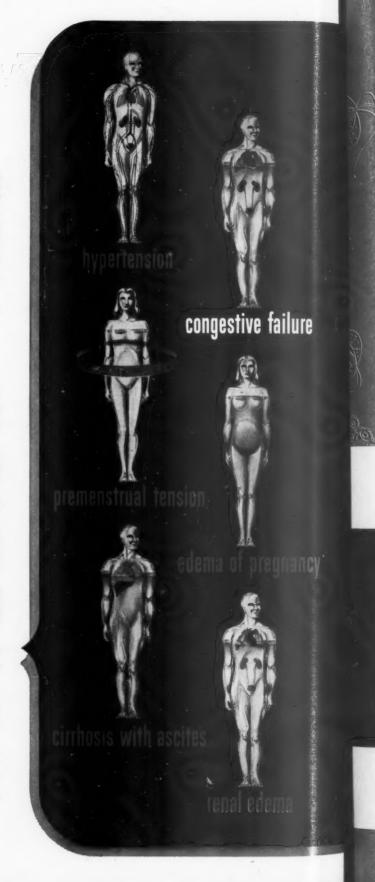
a continuing and consistently outstanding record of safety and efficacy in:

Supplied: 250 mg, and 500 mg, scored tablets DIURIL (Chlorothiazide). DIURIL is a trademark of Merck & Co., INC. Additional information is available to the physician on request.



MERCK SHARP & DOHME Division of Merck & Co., Inc., Philadelphia 1, Pa.

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BETADINE

VAGINAL GEL · VAGINAL DOUCHE

#### BETADINE

brand of Povidone-lodine, possesses broad-range germicidal activity against fungi, yeasts, bacteria, protozoa, and viruses. In the vaginal tract Betadine Vaginal Gel and Betadine Vaginal Douche kill trichomonas and monilia on contact and destroy common pathogens. Betadine is virtually nonirritating to vaginal mucosa.

#### indicated-

in the treatment of trichomoniasis, moniliasis and nonspecific vaginitis.

#### advantages:

- · almost immediate relief from leukorrhea, pruritus; diminishes malodor-
- · unsurpassed broad-range microbicidal activity
- · therapeutically active even in the presence of blood, pus, waginal secretions
- · wetting action to assist penetration into vaginal crypts and crevices

#### how to use:

In the office: Swab the vaginal vault with Betadine Antiseptic, full strength. prescribe Betadine Vaginal Douche for therapeutic use as follows: Two (2) tablespoonfuls to a quart of lukewarm water once saily by the patient at home, for six days. On the seventh day, the patient returns for re-examination and swabbing with Betadine Antiseptic; an additional week of therapeutic douching if necessary.

prescribe Betadine Vaginal Gel as follows: Insert one (1) applicatorful of Betadine Vaginal Gel each night, followed by a douche the next morning, through the entire menstrual cycle. If further therapy is warranted, the gel should be continued only during the actual menses days of the following two menstrual periods.

After the infection has been brought under control, the use of Betadine Vaginal Douche is recommended twice weekly at a dilution of one (1) tablespoonful to a quart of lukewarm water.

established in 1905

TAILBY-NASON COMPANY, INC., Dover, Delaware

BETADINE VAGINAL GEL 3 OZ TUBE WITH APPLICATOR

BETADINE® VAGINAL DOUCHE

8 OZ. BOTTLE

# Established Standard Therapy in Hypertension\*

alseroxylon, 2 mg.

#### \*Because

Rauwiloid provides effective Rauwolfia action virtually free from side effects...the smooth therapeutic efficacy of Rauwiloid is associated with significantly less-toxicity than reserpine...and with a lower incidence of depression. Tolerance does not develop.

Rauwiloid is initial therapy for every hypertensive patient. ... Dosage adjustment is never a problem...

When more potent drugs are needed, prescribe one of the convenient single-tablet combinations

alseroxylon 1 mg, and alkavervir 3 mg.

OI

alseroxylon 1 mg, and hexamethonium chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.



Northridge, California

just two tablets

at bedtime

After full effect

one tablet

#### NEW from Mead Johnson

relieves
painful
menstrual cramps
by relaxing
uterine spasm
or hypermotility



-vascular relaxant

## Pronounced vā.zō.DY-LAN

Mead Johnson is proud to announce the introduction of VASODĪLAN—an unusual new compound with myo-vascular relaxant action valuable in many fields of medicine. The unique myo-vascular action of this agent is manifested by selective relaxant effects on smooth muscle, predominantly in the uterus, the peripheral vascular and the cerebrovascular beds.

Notably safe, VASODĪLAN is now available to obstetricians and gynecologists for its benefits as a nonhormonal uterine relaxant in dysmenorrhea.

#### dosage and administration

For dysmenorrhea give 1 or 2 tablets (10 to 20 mg.) three or four times daily beginning 24 to 72 hours prior to the period. If pain is already present, give 2 tablets stat and repeat three or four time: daily until relief is obtained. There are too known contraindications to oral administration of VASODĪLAN in recommended doses.

#### supplied

As 10 mg. tablets and in 2 cc. ampuls containing 10 mg. (5 mg./cc.) for intramuscular use.

#### Clinically Validated

In one study\* pelvic cramping was relieved or averted in 27 of 33 known dysmenorrhea cases. There were no side effects sufficient to require cessation of oral dosage in this series.

\*Voulgaris, D. M.: Dysmenorrhea - Treatment with Isoxsuprine, to be published.

Relaxant effect of VASODILAN on isolated strip of human

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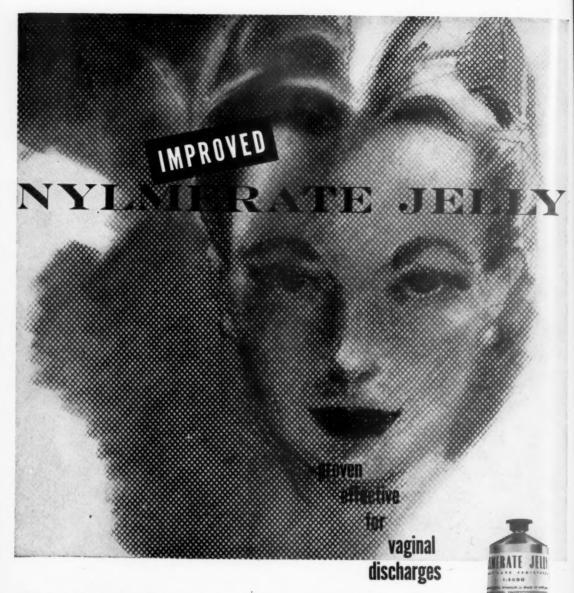
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## Concomitant measure: as a prophylaxis

NYLMERATE Solution Concentrate as a vaginal douche

- Therapeutic (Bactericidal and trichomonacidal)
- Acidic (4.1 pH in dilution)
- Reaches innermost recesses via low surface tension
- Use...twice daily (1 capfull to 2 quarts water)
- Economical
- Available only on your prescription (Eliminates possibility of excessive or unwarranted vaginal douching)

Specify pint bottles with measuring cap (Nylmerate: A brand of phenylmercuric acetate)



Check these important features of NYLMERATE

- Positive Trichomonacidal and Monilicidal action
- Symbiotic organisms eradicated by its bactericidal potency
- Low surface tension allows for deep epithelial cell penetration
- Re-establishes normal vaginal flora and prevents recurrences
- Simple to use...morning and night applications, including treatment during menstrual period

Prescribe: "Nylmerate Jelly with applicator" 3 oz. and 5 oz. tubes



Papanicolaou Stains standard for cytodiagnosis



Ortho Pharmaceutical Corporation

, N. Y.

RARITAN, NEW JERSEY



### "...SPINAL ANESTHESIA ... used wisely and properly.

should produce less complications than any other form of anesthesia."

for dependable spinal anesthesia

## PONTOCAINE

"....the most universally satisfactory and adaptable for the production of spinal anesthesia of a wide variety of types. Whether the 1 per cent, 20 mg. ampul solution or the Niphanoid preparation is used is a matter of preference."1

Spinal anesthesia with Pontocaine is safer and much more economical\* than with most forms of general anesthesia.

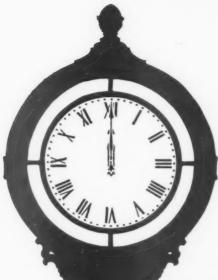
Pontocaine is available as

- 10, 15 and 20 mg. Niphanoid\* ampuls
- 1% solution, ampuls of 2 cc. (20 mg.)
- 0.3% hyperbaric solution in dextrose, ampuls of 5 cc. (15 mg.)
- 0.2% hyperbaric solution in dextrose for saddle block, ampuls of 2 cc. (4 mg.)
- 0.25% hyperbaric solution in dextrose for saddle block, ampuls of 2 cc. (4 mg.), Amptainers of 2 cc. (4 mg.)
- 0.15% solution for caudal and infiltration analgesia, vials of 100 cc.

Also available: 250 mg. Niphanoid ampuls for preparing solutions for caudal, infiltration or nerve block ana

- pp. 3, 22.
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  an. R. A.: Ross, E. F., Costley, E. C.: Western J. Surg., \$5,375.

inthition LABORATORIES . NEW YORK 130M.Y.



keeping appetite in check around the clock **PRELUDIN**°

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1956.

**ENDURETS** 

prolonged-action tablets

New long-acting PRELUDIN ENDURETS offer you a new method...a more convenient method... of administering this well-established, reliable appetite-suppressant. The new ENDURETS form virtually eliminates the vexing problem of the forgotten dose because... just one PRELUDIN ENDURET taken in the morning generally curbs the appetite throughout the day.

PRELUDIN ENDURETS afford greater convenience for your patient... added assurance to you that medication is being taken as prescribed.

PRELUDIN® (brand of phenmetrazine hydrochloride) ENDURETS,  $\tau$ . $^{\mathrm{M}}$ . Each ENDURETS prolonged-action tablet contains 75 mg. of active principle.

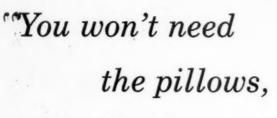
PRELUDIN is also available as scored, square pink tablets of 25 mg. for 2 to 3 times daily administration.

Under license from C. H. Boehringer Sohn, Ingelheim.

ENDURETS IS A GEIGY TRADEMARK

**GEIGY** 

ARDSLEY, NEW YORK



Mrs. Smith"

When hemorrhoids disturb

an otherwise smooth

pregnancy, a touch of

Americaine relieves the pain.

in minutes...for hours!

Nothing relieves surface pain like



(Ethyl-p-aminobenzoate, ASL)

**Topical Anesthetic Ointment and Aerosol** 



Send for samples

ARNAR-STONE LABORATORIES, INC., Mount Prospect, Illinois

the true specific for monilial vaginitis

## GENTIA-JEL

CURES ARE QUICKER Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrence. IMMEDIATE RELIEF This soothing jel provides fast, gratifying relief of vulvar itching and burning... destroys fungi and bacteria. COMPLETE COVERAGE Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia.



start therapy
with GENTIA-JEL
... it works
when others fail

## GENTIA-JEL

## the true specific for monilial vaginitis

Gentian violet is the most effective agent known for the destruction of Monilia albicans. Numerous nonstaining preparations have been used in treating vaginal moniliasis but have proven far less effective than gentian violet.

Gentia-jel's effectiveness is proved by its rate of cures during the last trimester of pregnancy, when mycotic infections are most difficult to cure. Gentia-jel is shown to be over 93% clinically effective, and has been used successfully in hundreds of cases refractory to other therapies.

Monilial reinfection is avoided with Gentia-jel by eliminating two major causes: (1) there is no manual introduction of tablets or suppositories into the vagina and (2) applicators are never reused, but discarded.

And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators.

WHY WAIT UNTIL OTHER THERAPIES FAIL.
START YOUR PATIENTS WITH GENTIA-JEL

WESTWOOD PHARMACEUTICALS

**Buffalo 13, New York** 



during pregnancy or lactation make sure of dietary adequacy with new low cost...

Mol-Iron Prenatal

ONLY 1 tablet daily, 1/2 the usual cost, phosphorus-free, 12 vitamins plus 10 minerals

The clinical superiority of MOL-IRON for the correction of iron deficiency during pregnancy has been established by more published reports than are available for any other iron preparation.

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

# IN STRESS CONDITIONS CIICH AC Spontaneo

AS Spontaneous abortion
Inflammatory diseases
Infectious diseases
Cardiovascular diseases
Metabolic diseases

## CAPILLARY AND VASCULAR DAMAGE ARE COMMON FINDINGS

In these stress conditions whether caused by nutritional deficiencies, environment, drugs, chemicals, toxins, virus or infections

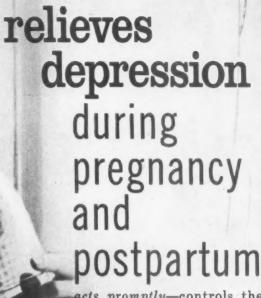
#### HESPERIDIN, HESPERIDIN METHYL CHALCONE or LEMON BIOFLAVONOID COMPLEX

are indicated as therapeutic adjuncts for the control and management of the associated capillary and vascular damage.

Sunkist and Exchange Brand Hesperidin and Lemon Bioflavonoid Complex are available to the medical profession in specialty formulations developed by leading pharmaceutical manufacturers.

#### **Sunkist Growers**

PRODUCTS SALES DEPARTMENT PHARMACEUTICAL DIVISION ONTARIO, CALIFORNIA



acts promptly—controls the syndrome of mental depression without C.N.S. excitation; reduces depressive rumination and crying; restores natural sleep without barbiturate-like hangover.

significantly different—unlike amine-oxidase inhibiting energizers, Deprol produces no liver toxicity and does not adversely affect blood pressure; unlike C.N.S. stimulants, Deprol has no depressive aftereffects, does not cause insomnia or depress appetite.

## Deprol\*

Usual starting lablet q.i.d. When this dose may ually increased up lets q.i.d.

Each tablet was 400 mg. mepro-

bamate and 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl).

Supplied: Bottles of 50 scored tablets.

1. Current personal communications; in the files of Wallace Laboratories. 2. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride.J.A.M.A.166:1019, March 1, 1888.

BOXATORIES, New Brunswick, N. J. Literature and samples on request

TTRADE-MARK

NEW

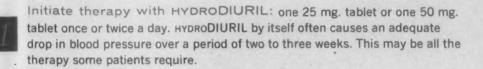
## HYDRO DU GENTHANDE

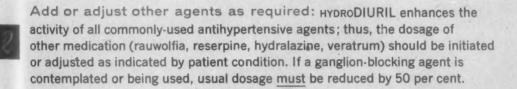
simplifies\* and improves any regimen for hypertension



## \*it's as easy as 1, 2, 3 to use

(HYDROCHLOROTHIAZIDE)





Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

Supplied: 25 mg, and 50 mg, scored tablets hyperodiuril (Hydrochlorothiazide) bottles of 100 and 1,000. Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., Inc. Trademarks outside the U S.: DICHLOTRIDE, DICLOTRIDE, HYDROSALURIC.



THIAZIDE)

MERCK SHARP & DOHME, Division of Merck & Co., Inc., Philadelphia 1, Pa.

AFTER FIRST STAGE

A SINGLE INJECTION

AFTER DELIVERY

LACTATION SUPPRESSED NO COMPLICATIONS





## DELADUMONE 2X

CONVENIENT OPTIMALLY BALANCED LONG-ACTING of lactation, Deladumone 2X contains the same "optimally balanced, long-acting combination" of testicular and follicular hormones provided by Deladumone in double the potency. "...[Deladumone] compares very favorably with other preparations in use for the inhibition of lactation and has the additional advantage of requiring only a single intramuscular injection." 2

Especially designed for convenient suppression

MORE EFFECTIVE THAN THE ORAL MEDICATION

"When employed in an adequate dosage at the proper time, the need for analgesics to control the breast symptoms is practically eliminated.... The use of Deladumone appears to essentially eliminate the undesirable withdrawal reaction or secondary breast engorgement that occasionally follows the cessation of oral medication."

NOTABLY FREE FROM UNWANTED EFFECTS

"... the balance of the hormonal components in Deladumone is such that it is possible to administer this preparation in a sufficiently large dose to prevent lactation without affecting the involution of the uterus, the character of the lochia, or the restoration of normal ovarian function."

Supply: Each cc. of Deladumone 2X provides 180 mg. testosterone enanthate and 8 mg. estradiol valerate dissolved in sesame oil. Vials of 2 cc.

Dosage: 2 cc. given as a single intramuscular injection preferably at the end of the first stage of labor or else immediately upon delivery.

1. Lo Presto, B., and Caypinar, E. Y.: J.A.M.A. 169:250 (Jan.) 1959. 2. Stein, W. W.: Am. J. Obst. & Gynec. 76:108 (July) 1958. 3. Watrous, J. B. et al.: J.A.M.A. 169:246 (Jan.) 1959.

**SQUIBB** 



Squibb Quality - the Priceless Ingredient

DELADUMONE . IS A SQUIBB TRADEMARK

### ight from the start!

the "right choice" antibiotic for use in

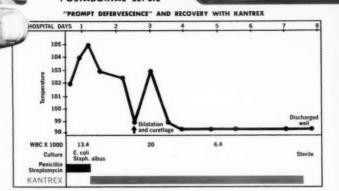
- skin, soft tissue and post-surgical infections
- genito-urinary infections
- respiratory tract infections due to staph or "gram-negatives"

KANANYCIN SULFATE INJECTION
INJECTION

- rapidly bactericidal not merely bacteriostatic
- minimizes emergence of bacterial resistance
- clinically safe in specified dosage
- effective against many organisms resistant to other antibiotics

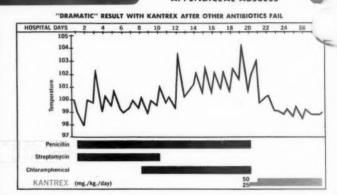
For prompt therapeutic results, KANTREX is the "right cloice" antihiotic to use in infections due to staph or "gram-negt ives"

#### POSTABORTAL SEPSIS

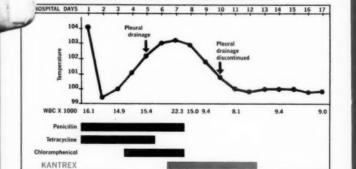


2 other antibiotics had proved ineffective. No toxic effects were observed.

#### APPENDICEAL ABSCESS



#### STAPH PNEUMONIA



KANTREX SUCCESSFUL: 3 OTHER ANTIBIOTICS INFEFECTIVE

in respiratory tract infections

ant with pneumonia, pycrompt beneficial effect and mevential recovery with CANTREX after 3 other antibiotics had proved unsuccessful. "No serious untoward reactions were observed."

—Riley, H. D., Jr.: Antibiotics Aunual 1968-1969, p. 623.

Willes Charles and the Krist Hally.

PRECAUTION: In patients with renal insufficiency, dosage should be reduced to avoid the risk of ototoxicity. See package insert for details.

SUPPLY: Available as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

EANTREX injection, 0.5 Cm. kanomycin (as sulfate) in 2 ml. volume.

EANTREX injection, 1.0 Cm. kanomycin (as sulfate) in 3 ml. volume.

KANTREX INJECTION KARANYCIN SULFATE INJECT



BRISTOL LABORATORIES INC., Syracuse, New York

KANTREX sensitivity discs and comprehensive literature available on request.



treats more patients more effectively...

Of 45 arthritic patients who were refractory to other corticosteroids\*

22 were successfully treated with Decadron 1,2

- 1. Boland, E. W., and Headley, N. E.: Paper read before the
- Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958. 2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
- \*Cortisone, prednisone and prednisolone.
- DECADRON is a trademark of Merck & Co., Inc.

Additional information on DECADRON is available to physicians on request.



ight cooice n-negaives

MSD Merck Sharp & Dohme

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

for your G.U. FREEDOM patients

## FURADANTIN

brand of nitrofurantoin

IN
SEVEN YEARS
NEGLIGIBLE
DEVELOPMENT
OF BACTERIAL
RESISTANCE
WITH
FURADANTIN

#### rom pain, infection and drug-induced complications

#### FREEDOM FROM PAIN AND INFECTION

"Nitrofurantoin [FURADANTIN] was effective clinically, with a pronounced improvement, indicated by the appearance of the urine as well as by verbal commendation by the patient, within 24 to 36 hours. . . . Some of these patients with seemingly impossible cases were cured of their infection."

"During the initial week of therapy, when the dose of nitrofurantoin was 100 mg. four times a day, the urine became free of pus and bacteria. Symptoms of urinary frequency, urgency, and dysuria were relieved."<sup>2</sup>

#### FREEDOM FROM DRUG-INDUCED COMPLICATIONS

- No significant development of bacterial resistance in over 7 years.
- No irreversible toxic effects on kidneys, liver, blood-forming organs or central nervous system ever reported.
- No monilial superinfection or staphylococcic enteritis ever reported.
- No fatalities from Furadantin therapy; the margin of safety is 90 to 1.
- "The drug was given continuously and safely for as long as three years." 2

"FURADANTIN has characteristics that make it a valuable drug for long-term administration to control urinary tract infection. These include its lack of toxicity, wide range of antibacterial effectiveness, and reduced tendency to induce development of bacterial resistance to the drug." 8

AVERAGE FURADANTIN ADULT DOSAGE: One 100 mg, tablet q.i.d. taken with meals and at bedtime with food or milk. Available as Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: I. Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. 160:1221, 1956. 2. Lippman, R. W., et al.: J. Urol., Balt. 80:77, 1958. 3. Marshall, M., Jr., and Johnson, S. H., III: J. Am. M. Ass. 169:919, 1959.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides o, N EATON LABORATORIES, NORWICH, NEW YORK





#### In Urinary Tract Infections

#### "Thiosulfil"

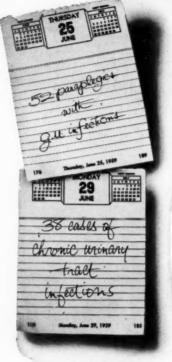
#### ...for prolonged use

"Thiosulfil' is a highly soluble sulfonamide derivative which can be administered effectively over a long period of time with minimal toxic manifestation."

> Cottrell, T.L.C.; Rolnick, D., and Lloyd, F. A.: Rocky Mountain M.J. 56:66 (Mar.) 1959.

"It ['Thiosulfil'] is useful for palliation in chronic urinary tract infections that are due to pathological conditions which cannot be cured. The drug can be taken over a long period of time with practically no untoward side reactions."

2. Barnes, R. W.: J. Urol. 71:655 (May) 1954.



#### "Thiosulfil"

#### ...well tolerated

"Thiosulfil' was remarkably well tolerated, there being no discontinuation of therapy due to untoward effects, and very few mild reactions were noted.... Thiosulfil' is a very valuable adjuvant in the treatment of common urinary infections..."

 Bourque, J. P. and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1953.



# 

Continued from preceding page

#### "Thiosulfil"

#### ... safe, effective

"Clinical trial appears to indicate that the drug ['Thiosulfil'] can be tolerated where other sulfa drug cannot and that it is effective where some others are not....The drug has been given with good results in the presence of urinary retention and severe uremia."

4. Goodhope, C. D.: J. Urol. 72:552 (Sept.) 1954.



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"Thiosulfil"

... potent antibacterial agent

"... Thiosulfil' is an effective chemotherapeutic agent in urinary tract infections.... there was only one failure in the 'Thiosulfil' treated acutely infected group (31 patients)."

> Hughes, J.; Coppridge, W. M., and Roberts, L. C.: South. M.J. 47:1082 (Nov.) 1954.

In difficult cases of paraplegics with urinary tract infections, "'Thiosulfil' was ineffective in only 7 per cent [93% effective] of the urinalyses as contrasted to 28 per cent [72% effective] of the urines on [sulfisoxazole] therapy."

 Cottrell, T. L. C.; Rolnick, D., and Lloyd, F. A.: Rocky Mountain M.J. 56:66 (Mar.) 1959.

"Thiosulfil" delivers more therapeutic impact at site of infection than any other single or combined sulfa compound. Higher urinary concentrations are achieved. 98% of the drug is present as free, active (nonmetabolized) sulfa<sup>6</sup>...a most efficient sulfa drug with outstanding patient toleration.<sup>4</sup>

 Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, April 6-9, 1959, San Francisco, California.

### "Thiosulfil"

Usual dosage: Adults, two tablets or two teaspoonfuls q.i.d.

Supplied: Tablets: No. 785 - 0.25 Gm. per tablet (Scored). Bottles of 100 and  $1{,}000$ .

Suspension: No. 914-0.25 Gm. per 5 cc. (teaspoonful). Bottles of 4 and 16 fluidounces.

#### also available: "Thiosulfil"-A

BRAND OF SULFAMETHIZOLE WITH PHENYLAZO-DIAMINO-PYRIDINE HOL in urinary tract infection when analgesia is desired

"Thiosulfile-A — each tablet contains: 0.25 Gm. sulfamethylthiadiazole and 50 mg, phenylazo-diamino-pyridine HCl.

Usual dosage: Adults, two tablets q.i.d.

Supplied: Tablets: No. 784 - Bottles of 100 and 1,000.



AYERST LABORATORIES

New York 16, N. Y. • Montreal, Canada

5939

August, 1959

Page 75

## In female urethritis age makes a difference

#### BEFORE THE MENOPAUSE,

localized urethral infection is highly prevalent but "easily overlooked" because pain and discomfort are frequently referred to other areas.

#### FURACIN® INSERTS (formerly Furacin Urethral Suppositories)

are antibacterial...anesthetic...gently dilating...provide rapid control of both pain and infection<sup>2</sup>...0.2% Furacin and 2% diperodon•HCI (an efficient local anesthetic), in a water-dispersible base. Each hermetically sealed in silver foil, box of 12.

#### AFTER THE MENOPAUSE.

estrogen deficiency leads to atrophy of the urethral mucosa, irritation, increased susceptibility to infection...a frequent source of pelvic distress.<sup>3</sup>

#### **FURESTROL® SUPPOSITORIES**

are estrogenic as well as antibacterial, anesthetic and gently dilating... provide "progressive histologic normalization" and prompt symptomatic relief<sup>4</sup>... 0.2% Furacin, 2% diperodon•HCl, and 0.0077% (0.1 mg.) diethylstilbestrol, in a water-dispersible base. Each hermetically sealed in orchid foil, box of 12.

REFERENCES: 1. Barrett, M. E.: J. M. Assoc. Alabama 26:144, 1956. 2. Youngblood, V. H.: J. Urol., Balt., 70:926, 1953. 3. Youngblood, V. H.; Tomlin, E. M.; Williams, J. O. and Kimmelstiel, P.: Tr. Southeast. Sect. Am. Urol. Assoc., Atlanta, Ga. (Apr. 7-11) 1957, p. 40-43. 4. Youngblood, V. H.; Tomlin, E. M. and Davis, J. B.: J. Urol., Balt., 78:150, 1957.

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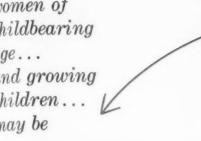
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RICS

women of childbearing age... and growing children . . . may be





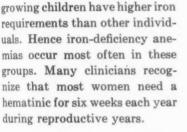




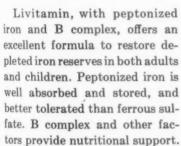
#### OVERDRAWN AT THE BLOOD BANK



THREJ BANK



Women of menstrual age and







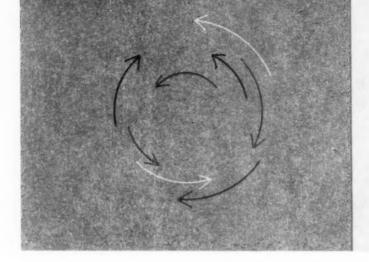
### LIVITAMIN

FORMULA: Each fluidounce contains: Iron peptonized 420 mg. (Equiv. in elemental iron to 71 mg.) Manganese citrate, soluble 158 mg. Thiamine hydrochloride 10 mg. Riboflavin 10 mg. Vitamin B<sub>12</sub> Activity 20 mcg. (Derived from Cobalamin conc.) Nicotinamide 50 mg. Pyridoxine hydrochloride 1 mg. Pantothenic acid 5 mg. Liver fraction 1 2 Gm. Rice bran extract 1 Gm. Inositol 30 mg. Choline 60 mg. SUPPLIED IN LIQUID OR CAPSULE.

with Peptonized Iron

#### The S.E. MASSENGILL Company

BRISTOL, TENNESSEE . NEW YORK . KANSAS CITY . SAN FRANCISCO



Livitamin assures patient acceptance because it is highly palatable. Peptonized iron provides a virtually predigested form of iron. Recent studies\* show peptonized iron has these advantages:

- Rapid response in iron-deficiency anemias
- Non-astringent
- Absorbed as well as ferrous sulfate
- Better gastric toleration than ferrous sulfate
- Less constipating than ferrous sulfate



... the preferred hematinic

\*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

The S. E. MASSENGILL Company BRISTOL, TENNESSEE

NEW YORK . KANSAS CITY . SAN FRANCISO

#### FOUND: a dependable solution to

"the commonest gynecologic office problem"

"VULVOVACINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . . "
Energy, J. E.: Am. J. Obet. 77:155, 1959

### TRICOFURON°

Improved

- · Swiftly relieves itching, burning, malodor and leukorrhea
- Destroys Trichomonas vaginalis, Candida (Monilia) albicans,
   Haemophilus vaginalis
   Achieves clinical and cultural cures
   where others fail
   Nonirritating and esthetically pleasing

#### 2 steps to lasting relief:

- 1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.
- 2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menetrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

Rx new box of 24 suppositories with applicator for more practical and economical therapy.

NITROFURANS—a unique class of antimicrobials EATON LABORATORIES, NORWICH, NEW YORK IRON THERAPY...WELL TOLERATED ....EVEN ON AN EMPTY STOMACH!

excellent results in over 11,000 CASES

ferronord

(brand of ferroglycine sulfate complex)

Page 80

Am. J. Obst. & Gynec

- serum response in 3 hours
- clinical response in days
- between-meal administration for better utilization
- WITH SIDE EFFECTS INSIGNIFICANT<sup>1-8</sup>

48 patients -- serum iron rose rapidly. Hb. response prompt

given on empty stomach in all cases-no gastric upset, diarrhea or constipation were found

91 patients<sup>2</sup>—significant reticulocyte response in 6 days on 2 tabs. t.i.d. in moderate hypochromic anemia—found extremely useful

even in those with peptic ulcer, gastritis, lack of side effects was reported as quite impressive -slight gastric upset in one patient

102 patients3 -a remarkably sharp rise in hemoglobin levels was demonstrated

one complaint of mild constipation

62 patients - reported to be a real advance in iron therapy

2 instances of G.I. upset disappeared with dosage adjustment

563 patients - found to be efficiently absorbed and to provide predictable clinical results

only eight cases of mild intoleranceno side effects even in patients with peptic ulcer

120 patients - peak reticulocyte response on fifth day

not a single complaint of upset, FERRONORD taken on empty stomach in all cases

41 patients - average daily Hb. rise of 1.6%

well tolerated in peptic ulcer and gastritis patients-given on empty stomach in all cases

10.016 patients - Hb, response excellent, average treatment period 4-6 weeks

only 4.39% of cases reported any side effectsusually adjusted with dosage

#### DOSAGE SCHEDULE



Average adult dose: initially, 2 tabs. b.i.d.; severe cases, 2 tabs. t.i.d.

Maintenance dose, 1-2 tabs daily. Each FERRONORD tablet supplies 40 mg. of ferrous



FERRONORD Liquid, 60 cc. dropper bottles, 40 mg. iron per cc.

#### BIBLIOGRAPHY:

BIBLIOGRAPH X:

1. Dwyer, T. A.: Clin. Med. 4:457, 1957. 2. Pomeranse, J., and Gadek, R. J.: New England J. Med. 257:73, 1957. 3. Clancy, J. B.; Aldrich, R. H.; Rummel, W., and Candon, B. H.; Am. Pract. & Digest Trent. 5:1948, 1957. 4. O'Brien, T. E.; Oneraco, R. R.; Dwyer, T. A., and Candon, B. H.: West. J. Surg. 65:29, 1957. 5. Frohman, I. P., and others: Scientific Exhibit, Sixth Congress Internat. Soc. Hemat., Boston, Mass., Aug. 26-Sept. 1, 1956. 6. Wagner, H.: Landarst 21:496, 1955. 7. Jorgensen, G.: Arzti, Wchnschr. 10:82, 1955. 8. Aldrich, R. H.; Pomeranse, J.; Clancy, J. B., and others: Scientific Exhibit, A.M.A. Meeting, June, 1957, New York, N. Y.

FERROMORO® (SRAND OF FERROSLYCINE SULFATE COMPLET) PAT. PENDING



Nordson Pharmaceutical Laboratories, Inc., Irvington, New Jersey

to relieve pain of dysmenorrhea...



remember

ZACTIRIN will return many patients suffering from the pain of dysmenorrhea to normal physical activity. Its analgesic effect is equivalent to that of codeine, yet it is non-narcotic, hence has no addiction liability. Side-reactions are mild and low in incidence.

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.



for your obstetrical and gynecological patient

BACULIN VAGINAL TABLETS

FUNGICIDAL ... BACTERICIDAL ... PROTOZOICIDAL COMPREHENSIVE TREATMENT OF VAGINAL INFESTATION.

A single BACULIN vaginal tablet generally destroys the causes of vaginitis, namely Trichomonas Vaginalis, Candida Albicans, and non-specific organisms. Prescribe BACULIN vaginal tablets in your next case of non-venereal vaginitis.

BANAUSEA

ANTINAUSEANT, ANTIEMETIC — BAN NAUSEA AND YOMITING OF PREGNANCY . . . SAFELY . . . EFFECTIVELY . . . ECONOMICALLY.

Just prescribe BANAUSEA tablets, one upon arising and one at bedtime. Turn your patients' blue mornings pink with BANAUSEA tablets.

Samples upon request.

Rolemondo I Poño E F. Mad Timos 89,091 1954

Amfre-Grant, Inc., Brooklyn 26, N. Y.

#### Analgesia with a plus

In Obstetrics, Surgery, Relief of

## MEPER



MEPERGAN combines PHENERGAN® HCl (promethazine HCl, Wyeth) with meperidine HCl. Both drugs have been widely employed in the PHENERGAN-meperidine regimen for sound perisurgical and obstetrical management. The merging of the two agents in MEPERGAN provides analgesia augmented by the many demonstrated values of PHENERGAN. These include the quelling of apprehension, the control of nausea and vomiting, the potentiation of barbiturates and narcotics, and the facilitation of anesthesia. An abundant clinical experience<sup>1-3</sup> confirms that:

- 1. MEPERGAN provides analgesia plus sedative, amnesic, antiemetic, antihistaminic, and potentiating actions
- 2. MEPERGAN produces analgesia reported to be twice as great as that of its meperidine content
- 3. MEPERGAN provides safe basal anesthesia
- 4. MEPERGAN permits smaller doses of anesthetics—important in surgery and obstetrics
- 5. MEPERGAN permits smaller doses of narcotic analgesics by promethazine potentiation—important in obstetrics, in postoperative pain control, and in intractable pain requiring extended use of narcotics
- MEPERGAN management is remarkably free of significant alteration in vital functions because it reduces the need for depressant agents—important for safety of obstetrical patient and baby

Severe Pain

meperidine-promethazine combined

Promethazine Hydrochloride and Meperidine Hydrochloride, Wyeth

In Obstetrics: MEPERGAN benefits both mother and infant.1-3 Providing predictable maternal sedation and analgesia, it markedly reduces the need for narcotics and eliminates the need for barbiturates in labor, thus reducing the likelihood of fetal distress. In addition, antiemetic protection is afforded, and shortening of labor has been consistently reported.1

In Perisurgical Care: MEPERGAN is useful in all forms of surgery.4-6 It may be used preoperatively for preparatory medication, during surgery as an adjunct to anesthesia, and postoperatively to control pain.

In Severe Pain: MEPERGAN is valuable for the relief of intense pain from various causes, including malignancy.5 Its narcotic-potentiating action often permits substantial reduction in the daily requirements for potent analgesics.

CAUTION: The package circular should be consulted before MEPERGAN is used. See particularly the statements on injection routes, dosage, precautions, and side-effects.

1. Carroll, J.J., and Moir, R.S.: J.A.M.A. 168:2218 (Dec. 27) 1958. 2. Gollin, H.A., et al.: Am. Pract. & Dig. Treat. 9:2001 (Dec.) 1958. 3. Potts, C.R., and Ullery, J.C.: A Scientific Exhibit. Presented at meeting of American College of Obstetricians and Gynecologists, Atlantic City, April 5-8, 1959. 4. Piserchia, E.G.: J. M. Soc. New Jersey 55:261 (June) 1958. 5. Light, G.A., et al.: J.A.M.A. 164:1648 (Aug. 10) 1957. 6. Weiss, W.A., and McGee, J.P., Jr.: Ann. Surg. 144:861 (Nov.) 1956.

\*Trademark



Philadelphia 1, Pa.

## An EDGE on them all

Cutting efficiency and maximum blade performance has always been the surgeon's first consideration when choosing a surgical blade. BARD-PARKER offers you a blade made with the same consideration in mind... a blade of carbon steel of course... so superior for fine cutting edges.

## B-P RIB-BACK Blades are now available ....

in the Puncture Proof Sterile Blade package that can be autoclaved.



in the RACK-PACK package—blades pre-racked ready for sterilization.

in the CONVENTIONAL package—six of one size in a rustproof wrapper. 1ts Sharp

Ask your dealer

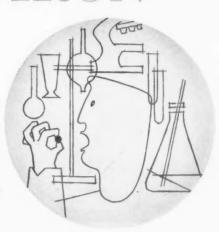


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# RLATED II



■ outstandingly free from g.i. irritation ■ does not stain teeth [when given as a liquid] a can be taken any time - between meals without irritation, or at mealtime without impaired utilization meantible with ulcer medication, and does not cause added irritation safest iron to have in the home because of chelate-controlled absorption and - clinically confirmed as an effective hematinic [Franklin et al.: J.A.M.A. 166:1685, 1958]

Trademark

the new way to give oral iron

CHELATED

Brand of Iron Choline Citrates

Tablets — 1 tablet t.i.d. furnishes 120 mg. iron Pediatric Drops - 1 cc. furnishes 25 mg. iron Liquid - 1 tsp. (5 cc.) furnishes 50 mg, iron also: CHEL-IRON PLUS Tablets — chelated iron plus B<sub>12</sub>, folic acid, other B vitamins, and C.





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"Chelate" describes a chemical structure in which metallic ions are "encircled" and their physicochemical properties thereby altered. Chelated iron (as iron choline citrate\*) is unusually soluble; nonionizable; not precipitated by variations in g.i. tract pH, protein, phosphate, or alkali; yet is readily available for hemopoiesis on physiologic demand.

QU. S. PAT. 2.575.631

quick, accurate early pregnancy diagnosis...



new, 3-day oral test for pregnancy

## Pro-Duosterone®

anhydrohydroxyprogesterone 50.00 mg. activated by ethinyl estradiol 0.03 mg. per tablet

safe . . . physiologic . . . therapeutic

Pregnancy may now be diagnosed safely, simply and accurately in its earliest weeks by oral administration of Pro-Duosterone® tablets four times daily—with each meal and at bedtime—for only three consecutive days. In the nonpregnant patient uterine bleeding usually occurs 3 to 7 days after progesterone therapy. No bleeding occurs when pregnancy exists; on the contrary, gestation is protected. Moreover, in short-term functional amenorrhea regular menstrual cycles are usually restored by oral progestogen.

The speed and precision of this oral diagnostic test are unsurpassed, and "no laboratory equipment, animals, or specimens are needed." The 3-day, oral Pro-Duosterone test for pregnancy is also less costly than biologic methods. Finally, full diagnostic and therapeutic efficiency is assured by the small estrogen component of the Pro-Duosterone formula since "Progesterone has no action whatsoever in the absence of estrogens." Supplied: Bottles of 24 pink tablets. Roussel Corporation, 155 E. 44th St., New York 17

1. Hayden, G. E.: Am. J. Obs. & Gynec. 76:271, 1958. 2. New & Nonofficial Drugs: J.A.M.A. 168:181, 1958. 3. Page, E. W.: GP 9:53, 1954.



can't take iron...

## can take FERMALOX

tablets (RORER)

66... buffered ferrous sulfate in uncoated tablets... the best all-around medicament for use in iron deficiency states. 199

1. Price, A. H., et al: J.A.M.A. 167:1612, 1958.

FERMALOX is iron, buffered with Maalox-Rorer in uncoated tablets for use in anemia. Many patients, in whom intolerance to iron has been a problem, can take FERMALOX without difficulty. In iron therapy, FERMALOX offers three distinct advantages:

- Low Dosage—"..., satisfactory hematopoietic response... is obtained with 44% of the dosage of ferrous sulfate recommended by the Pharmacopeia of the United States."
- MINIMUM GASTRIC DISTURBANCES—"This reduced amount of iron, plus the buffering with (MAALOX-Rorer), accounts . . . for the almost complete absence of adverse reactions . . ."
- MAXIMUM ABSORPTION—The high iron utilization supplied by FERMALOX tablets is explained by rapid disintegration in the stomach,

"making the iron immediately available for absorption in the stomach and duodenum."

Each Fermalox tablet contains: Iron sulfate, principally ferrous, 200 mg.; Maalox-Rorer (magnesium-aluminum hydroxides) 200 mg.

Offered: bottles of 100 at prescription pharmacies.

Dose: 2 tablets daily for satisfactory hematopoiesis. May often be reduced to 1 tablet daily after 15 days.

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# What IS The Truth About Dietary Fats?

Recently a great deal of interest has been aroused on the question of a possible etiologic link between the ingestion of food fats and pathophysiologic changes in certain body tissues.

Basic research on this problem is being carried on throughout the world, the approach ranging from animal experimentation to biochemistry, to ethnological statistics.

In a number of instances the lay press has prematurely reported the findings of one research group or another, without the benefit of unbiased competent evaluation. Some scientific as well as lay articles have attempted to correlate inconclusive, fragmentary, and conflicting results, frequently leading to undesirable confusion.

The problem, however, is far from settled. If final results of this world-wide research establish beyond reasonable scientific doubt that fat intake is directly related to degenerative disease, accurate information should be provided for the profession so that in turn the public may be properly enlightened.

On the other hand, if conclusive evidence points to little or no etiologic relationship between fat ingestion and degenerative disease, it will become difficult for the scientific world to counteract the cumulative effects of misinformation on the public mind.

Furthermore, evidence is accumulating to indicate that lowering of the plasma cholesterol by limitation of dietary fat and by administration of unsaturated fatty acids may actually increase the deposition of cholesterol in the tissues.<sup>1</sup>

The obvious need at present is for basic research and proper evaluation as well as unprejudiced correlation of findings from all quarters, so that the medical profession as well as the public may be protected from the publicizing of premature and unwarranted conclusions.

#### STATEMENT BY NATIONAL RESEARCH COUNCIL

"A large amount of information has been made available in recent years relating fats to the causation of atherosclerosis, coronary artery disease, and other similar diseases. However, the data are so incomplete and conflicting that it is impossible to draw conclusions which are universally acceptable to nutritionists and medical authorities."

"Until it is clearer which fats are more desirable nutritionally and which, if any, are undesirable—major changes in American dietary habits are not to be recommended."

The Role of Dietary Fat in Human Health: National Academy of Sciences—National Research Council, Washington, D. C., Publication 575, 1958.

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Kuhl, W. J., Jr., and Cooper, J.: Exchangeable C<sup>14</sup>-Cholesterol Pool Size as an Index of Cholesterol Metabolism: Effect of Low Fat and Highly Unsaturated Fat Diets, Proc. Cen. Soc. Clin. Res., J. Lab. & Clin. Med. 52:919 (Dec.) 1958.

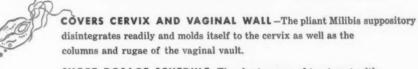
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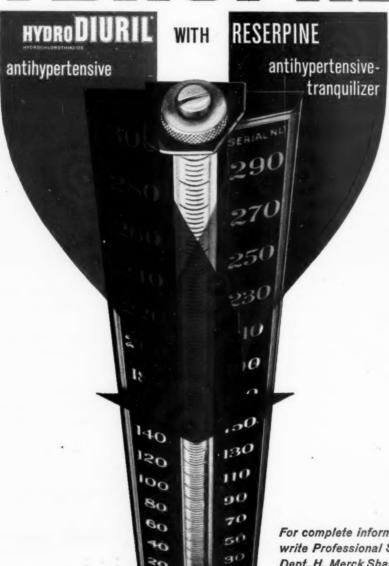
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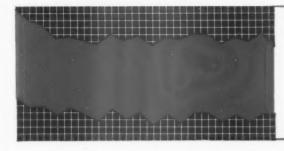
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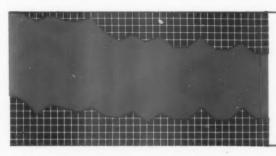
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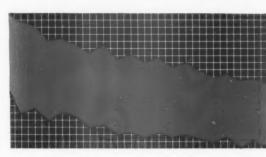
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1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.

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1. Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gynec. 9:703, June 1957.

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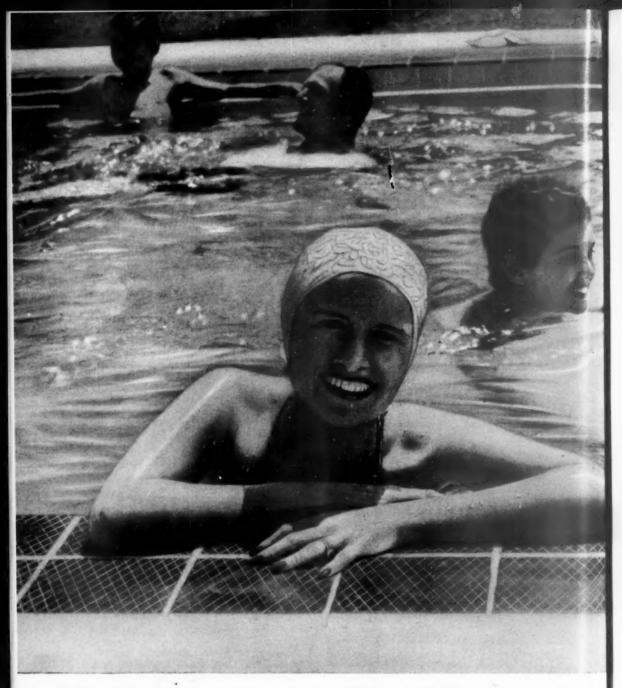
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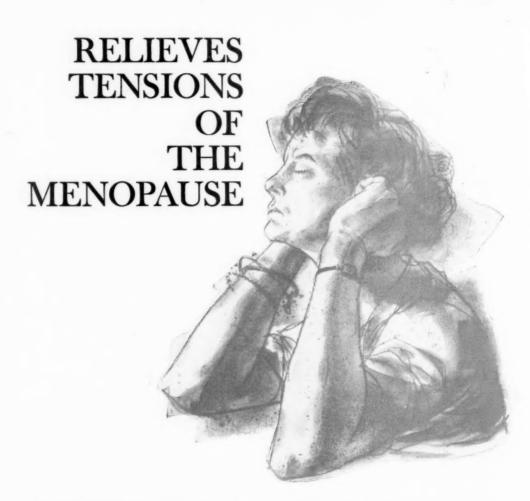
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1. Farquharson, R. F.: The menopausal patient. M. Rec. & Ann. 49:196, Feb. 1955.

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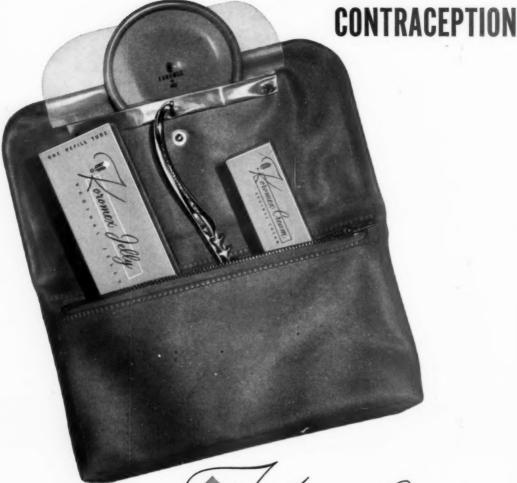
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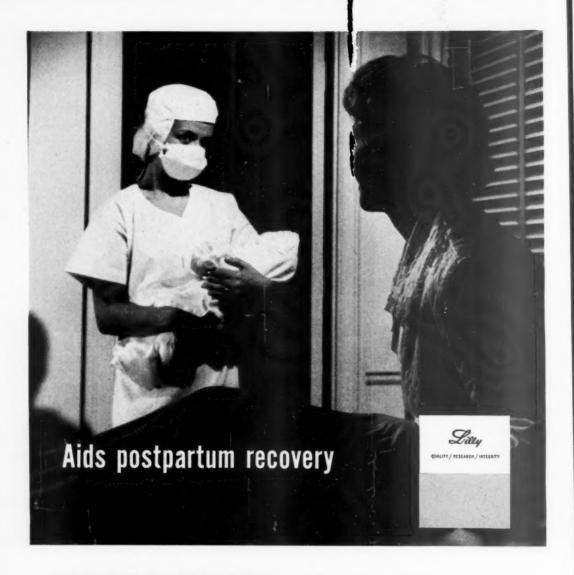
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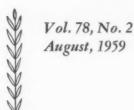


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#### OBSTETRICS AND GYNECOLOGY

Gynecology

NUCLEAR SEX AND GENITAL MALFORMATION IN 48 CASES OF RENAL AGENESIS, WITH ESPECIAL REFERENCE TO NONSPECIFIC FEMALE PSEUDOHERMAPHRODITISM\*

Peter J. Carpentier, M.D.,\*\*\* and Edith L. Potter, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital)

LARGE proportion of all individuals with malformations of the genital system exhibit abnormalities of other organs. The latter sometimes so dominate the clinical picture that genital or gonadal abnormalities are not noticed, or excite little interest, and it seems probable that in this way many abnormalities in sexual development have escaped detection in the past. As a consequence, careful examination of the genital system and the different sex characteristics might yield rewarding information if done systematically in all individuals with any variety of malformation. This seems particularly true when, as in renal agenesis, there is a much greater frequency in one sex, and the organs involved have a close ontogenetic relationship to the genital system. For this reason a study has been made of the different sex criteria and the associated genital malformations of 48 infants with complete bilateral renal agenesis on whom autopsy examinations were performed at the Chicago Lyingin Hospital. These findings have also been correlated with other observations on maldevelopment of the genitals, especially those found in female pseudohermaphrodites.

<sup>\*</sup>Supported in part by United States Public Health Service Grant for Medical Research 3166.

A sex characteristic which has proved very reliable and is referred to in this paper as nuclear sex was discovered by Barr.¹ He described a small chromatin body, about one micron in diameter, in the cell nuclei of human females and females of several animal species, which he was unable to detect in the cells of males. Although direct proof is still lacking, much indirect evidence justifies the opinion that this chromatin body, the so-called sex chromatin, is derived from heterochromatic portions of the XX chromosome complex and consequently is indicative of true genetic sex. This discovery has been responsible for important advances in the clinical investigation of certain syndromes associated with aberrations in sexual development.²-8 Methods have also been developed for identification of nuclear sex by the study of polymorphonuclear leukocytes in blood smears. Valuable retrospective studies have also proved possible since sex chromatin can be identified in tissue sections or vaginal smears that have been on file for many years.

One variety of malformation which, because of its uneven sex distribution, has been subjected to investigation of nuclear sex pattern is anencephaly. Approximately 90 per cent of such infants appear to be females and abnormalities of the gonads or reproductive system are rare. Polani and Claireaux<sup>13</sup> examined tissue cells from 4 male and 8 female anencephalic fetuses and found complete agreement between the chromatin pattern of the nuclei and the sex as indicated by the form of external and internal organs. Perrin and Benirschke<sup>14</sup> reported similar results in 27 female and 8 male anencephalic fetuses and included a description of the gonads in 27 cases. One of us (P. J. C.) in an unpublished series of 10 female anencephalic fetuses found a uniformly female-type nuclear pattern in oral and vulvovaginal smears.

Bilateral renal agenesis is another malformation in which one sex predominates, with about three-fourths appearing to be males. The only record of a comparison of sex determined by nuclear pattern and that resulting from inspection of the gonads and genital system in infants with this malformation is from Davidson and Ross<sup>15</sup> who found complete agreement in 4 males and one female. In view of these considerations it seemed worthwhile to extend this investigation to a larger series of eases.

The number of infants with bilateral renal agenesis who have been encountered on the autopsy service of the Chicago Lying-in Hospital is the largest group ever collected. Among almost 11,000 autopsies performed from 1935 to the present time on fetuses and newborn infants, 48 were on infants or fetuses who had no renal tissue. Twenty were observed before 1944 and were described in 1946<sup>16, 17</sup> and 10 more were added to this group in 1952.<sup>18</sup> The remainder were observed in the intervening years with none found in 1957 or 1958.

The present study is based on gross examinations of these infants as recorded at the time of autopsy and on microscopic study of tissue sections. Eighteen of the group were stillborn, half of them with variable degrees of maceration which at times rendered adequate postmortem examination and

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histologic investigation difficult or impossible. In addition, 5 of the 24 infants who were not born in this institution were dissected elsewhere and only tissue samples and a report of clinical and autopsy data were received for study.

In only 41 cases were tissue sections available for systematic investigation of the nuclear sex type, 2 having been lost and 5 being unsatisfactory because of maceration. From 2 to 10 sections were available in each case. All sections were carefully examined under a 40 and 60 mm, objective with a ×15 ocular giving a magnification of 600-900. Only well-outlined vesicular nuclei with homogeneously distributed chromatin were selected for study. The most satisfactory nuclei were found in young fibroblasts, in cells from skeletal, smooth and cardiac muscle, in adrenal cortex, and in basal layers of stratified epithelium. Cells of other organs, including the liver, were generally not satisfactory for this purpose. No attempt was made to determine the exact percentage of cell nuclei containing a sex chromatin body. Since in all tissues the majority of cells are unsuitable, counting the frequency with which the sex chromatin body can be recognized becomes relatively meaningless. Instead, it seems better to examine very critically the chromatin pattern of some 20 entirely satisfactory cells and to base one's opinion on these. Moreover, experience has led us to believe that a true sex chromatin body occurs exclusively in the female. Chromatin agglomerations, which cannot be distinguished from it even by an experienced observer, may occasionally be found in the male, but very rarely in suitable nuclei. Provided that the examiner has sufficient critical sense and has had adequate experience, essentially qualitative criteria are preferable to empirical, quantitative limits. In extensive material from sexually normal and abnormal patients, studied by one of us (P. J. C.) during the last 3 years, in which conclusions were almost always reached before the state of the patient was known, this method of approach has never given rise to confusion.

Among the 41 cases with suitable tissue sections, 10 presented female-type and 31 male-type nuclei. In every infant possessing male-type nuclei, the diagnosis of nuclear sex agreed with the reported genital and gonadal findings. Among the subjects with female-type nuclei, however, one (Case 4) had been registered as a male. In the remaining 9 females, internal genital organs, gonads, and nuclear chromatin pattern were concordant.

#### Diagnosis of Sex

Generally speaking, sex can be diagnosed in normal individuals from any characteristic present in one sex and absent in the other. This is ordinarily done at birth by simple inspection of the external genitals. However, in individuals in whom the possibility of sexual maldevelopment is suspected the different components of the sex pattern should be studied separately as their nor-

mal interrelationship may be lost.

It is now generally agreed that the nuclear chromatin pattern has replaced the gonads as the most important criterion of sex. However, it is important that all criteria for diagnosis of sex be included in any study of sexual abnormality. Inspection of the external genitals at birth, the gross and microscopic exploration of the gonads and other sex organs at operation or autopsy, and a study of the nuclear chromatin pattern in any available cells or tissues should be part of every investigation.

Table I. Infants and Fetuses in Whom the Correct Diagnosis of Sex by External Examination Was Difficult or Impossible

NUMBER	WEIGHT (IN GRAMS)	GENITAL ORGANS			NU- CLEAR	MAJOR ASSOCIATED MAL-
		EXTERNAL	INTERNAL	GONADS	SEX	FORMATIONS*
41608	1180	Absent	Male type	Testes anterior to symphysis	M	Sirenomelus, imperforate anus Type III, duodenal stenosis, absent descending colon, in- traventricular septal defect
56151	1310	Absent	Male type	Abdominal tes- tes	M	Sirenomelus, imperforate anus Type III, hypoplastic colon, single umbilical artery
52413	995	Absent	Male type	Abdominal testes	M	Sirenomelus, imperforate anus Type III, absent sigmoid and rectum, tetralogy of Fallot
54118	1040	Penis absent, scrotum pres- ent	Male type	Abdominal tes- tes, bilateral hydrocele	M	Sirenomelus, imperforate anus Type III, tracheoesophageal fistula, absent aortic arch, second of twins
46271	1790	Posterior tail- like penis and scrotum	Male type	Abdominal testes	M	Sirenomelus, imperforate anus Type III
47418	360	Absent	No tubes, uterus, or vagina	Abdominal gonads, prob- ably testes	_	Sirenomelus, imperforate anus Type III
38482	1645	Penis absent, scrotum pres- ent	Male type	Testes in scrotum	M	Imperforate anus Type III, absent sigmoid and rectum
52176	1230	Penis absent, half scrotum absent	Male type	Abdominal testes	M	Anorectal malformation Type I
545	1480	Penis normal, scrotum absent	Male type	Abdominal testes	M	Imperforate anus Type III
53132	1190	Rudimentary structure pos- sibly a clitoris	Rudimentary tubes and uterus, closed vagina	Normal ovaries	-	Imperforate anus Type III, colon terminating in vagina
491409	225	Hyperplastic clitoris or small penis	Normal tubes, no uterus or vagina	Normal ovaries	-	Imperforate anus Type III sigmoid and rectum absent
47357	1290	Normal penis and empty scrotum	Normal tubes, no uterus or vagina	Normal ovaries	F	Pseudohermaphrodite, imper- forate anus Type III, colon terminating in bladder (Case 1)
54120	1110	Normal penis and empty serotum	Normal tubes, no uterus or vagina	Normal ovaries	s F	Pseudohermaphrodite, imper- forate anus Type III, color terminating in bladder (Case 2)
51245	1580	Penis with ab- normal labia or scrotum	Hypoplastic tubes, no uterus or vagina	Small ovaries	F	Pseudohermaphrodite, sirenorelus, imperforate anus Type III, absent sigmoid and rectum (Case 3)
42258	1015	Hypoplastic penis and serotum	No tubes, uterus, or vagina	Abdominal "testes"	F	Pseudohermaphrodite, imperforate anus Type III, absent sigmoid and rectum, malformed hands and arms (Case 4)

<sup>\*</sup>The lungs were hypoplastic and the feet and legs were abnormal in position in all instances except where otherwise noted.

In our material the following correlations were made:

External Genital Organs.—In 33 infants, 25 males and 8 females, the external genitals were sufficiently normal for sex to be correctly diagnosed on external examination. In 11 others the external genitals were absent or abnormal and a positive diagnosis was impossible, and in 4 instances female pseudohermaphrodites (see case reports) were incorrectly diagnosed as males because of a penile urethra (Table I).



Fig. 1.—The only female infant with sirenomelus deformity. Note the penile structure with glans and terminal urethra, flanked by two skin folds.

Seven of the 15 infants with abnormal external genitals showed the sirenomelus deformity, characterized by a single lower extremity resulting from fusion of the lower limbs. Six of these were males; 4 had no external genital structures, one had a taillike appendage arising posteriorly from the lower end of the sacrum which proved to be a penis, and in another the penis was absent but an empty scrotum was present. Five possessed testes and male-type nuclei and one was an extremely macerated small fetus of 360 grams in which no uterus or Fallopian tubes could be found and which was consequently assumed to be male. The seventh infant in the sirenomelus series had a penile structure flanked by small folds (Fig. 1) which could be interpreted equally as rudimentary labia or an abnormal bifid scrotum. It proved to be female (Case 3) although before postmortem examination it was thought probably to be a male because of the penile urethra.

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ns cept Of the remaining 8 infants with marked abnormalities of the external genitals the gonads and the sex chromatin pattern agreed in indicating that 3 were male and 5 female. In 2 of the males the penis was absent: one had a normal scrotum, the other had what appeared to be a half scrotum in the right groin. In the third male the penis was normal but the scrotum was absent. Of the 5 females, 3 were considered males with undescended testes on external examination because of a penis with a central urethra and absence of anything resembling a vagina (Cases 1, 2, and 4). The fourth lacked external genitals, although a small structure thought possibly to be a rudimentary clitoris was present in one groin with a tiny depression 2 mm. deep lying beneath it. The fifth female was a 225 gram macerated fetus with a structure described as a small penis. This fetus was not included with the 4 pseudohermaphrodites because of the inability to determine unequivocally the character of this structure.

Gonads.—A gross description of the gonads was available in 43 of the infants. In 12 they were described as ovaries, in 30 as testes, and in one they were assumed to be testes, although a positive statement was impossible because of extreme maceration. Except for the one case described in Case 4 the gonads in every instance were in accord with the independently determined nuclear sex type.

A definite description of the gonads was not available in 5 but the infants were all stated to be male. In 3 of these the autopsy report did not specifically mention the gonads but all 3 had male-type nuclei. One original protocol and 2 sets of tissue sections could not be found.

Histologic sections of the gonads were available for study in 18 cases. In 6 they were ovaries and in 12 testes. The testes appeared normal in all except 2 instances where the testicular tubules were slightly hypoplastic. One of these was a sirenomelus with no external genitals and a malformed heart; the other was a twin with a long and angulated penis and multiple other anomalies, including imperforate anus, absent sacral and lumbar spine, extreme hypoplasia of the lungs, and webbing of the neck and knees. The ovaries were normal in all 6 cases.

#### Malformations of Genital Organs in the Two Sexes

#### Males .-

External genital organs: In addition to the 9 males with severe malformations described in Table I, 4 others had less marked disturbances in development of the external genitals. Three had a variable degree of elongation and angulation of the penis accompanied by anorectal anomalies and one had a slight hypospadias but the testes were in the scrotum and the anus and rectum were normal. The external genital development of the remaining 22 males appeared to be normal.

Internal genital organs: The location of the testes was specifically described in 25 of the total 35 males. In 12 both testes were located in the abdominal cavity, in one both were at the pelvic brim, and in another they were high in the usual location of the kidneys. In 5 they were incompletely descended and in 8 both were in the scrotum.

Although the description of the male genital ducts was often somewhat incomplete several essential facts emerge from the available data. A grossly normal or slightly hypoplastic epididymis and ductus deferens were present but the seminal vesicles were frequently lacking. Whenever the prostate could not be definitely identified grossly, microscopic evidence indicating at least a rudimentary development could generally be found in sections of the bladder neck region.

#### Females .-

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External genital organs: In addition to the 6 females described in Table I there were 7 others with malformations since no female had an entirely normal genital system. Excluding the one described in Table I which was thought to be a male with undescended testes, the following statements can be made, based on all 12 cases. The clitoris was small and rudimentary in one case, normal or presumably normal in 7, and hyperplastic in one. In the only female sirenomelus (Case 3) it had a penile appearance and in 2 others (Cases 1 and 2) it looked like a completely normal penis, with a patent urethra and was accompanied by a normal-looking empty scrotum.

A female-type urethral opening was present and patent in 7, hypoplastic in 2, and replaced by a penile urethra in 3.

Internal genital organs: A normal vagina with a normal orifice was present in only 2 infants but in one of these it ended blindly, due to the absence of the



Fig. 2.—Uterus bicornis duplex with double closed vagina.

uterus; in the other it communicated with a double uterus. In 8 infants no trace of vagina could be found. In the 2 remaining females the vagina had no external opening: in one it consisted of a small pouch containing the two cervices of the uterus bicornis duplex (Figs. 2 and 3) and in the other it was moderately dilated and filled with meconium because of a small communication with a blind-ending colon: the uterus was absent.

A uterus was missing in 8 infants, in 2 it consisted of two unfused, rudimen-

tary tissue knobs, and in 2 others of a uterus bicornis duplex.

The Fallopian tubes were more frequently normal than any other part of the female genital tract; this was the case in 8 of the 12 infants. In 3 they were hypoplastic, in another the right tube was normal and attached to the homolateral, knoblike uterine half while the left was an isolated structure ending free in the inguinal canal.

In 9 of the 12 recognized females the ovaries were normal. In 2 they were hypoplastic, flat, thin, and tapelike. In another they were large and elongated, had a combined weight of 2 grams, and contained many grossly

visible follicles.

# Case Reports

The following cases are those in which a female child was erroneously thought to be male on external examination because of a penile urethra.

Case 1.—47357. A stillborn Negro fetus weighing 1,290 grams and measuring 39.5 cm. in length, the fifth child of a 26-year-old woman who had had no prenatal care, was delivered precipitously from a breech position in the thirty-third week of pregnancy after an unattended labor of less than one hour. External examination revealed a face characteristic of renal agenesis with prominent epicanthic folds and ears low set at an angle and containing little cartilage, bilateral calcaneovalgus, an imperforate anus, and external genitals resembling those of a normal male with undescended testes.

The organs were normal except for the lungs which were hypoplastic, the kidneys and ureters which were both absent, and the colon which terminated in the sigmoid portion. This



Fig. 3.—From the same infant as in Fig. 2 showing organs in situ. The appearance of the adrenal glands is typical of renal agenesis.

communicated with the bladder through an extremely small opening. The bladder contained meconium which could be expressed from the penile urethra. The anus was imperforate. The vagina and uterus were absent although both Fallopian tubes and both ovaries were present. The lower ends of the tubes merged with the surrounding tissue and were not attached to each other or to anything that resembled a uterus.

The ovaries contained normal ova and early Graafian follicles (Fig. 4). The penile structure contained a urethra surrounded by erectile tissue (Figs. 5 and 6), and the base of the bladder had a few small glandlike structures suggestive of rudimentary prostate glands. The lungs were moderately hypoplastic and hemorrhage was present in the interstitial tissue. The chromatin pattern of nuclei in all sections was of the female type.

CASE 2.—54120. A white fetus weighing 1,110 grams, measuring 38.0 cm. in length, was born in the thirtieth week of pregnancy by breech extraction with manual aid. The mother was 20 years old and had 3 previous pregnancies, the first ending in a stillbirth,

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the second in neonatal death, the third in a healthy surviving child. No untoward symptoms were present during pregnancy, labor, or delivery. The infant was alive at birth but respiration could not be established and the heart stopped beating after 21 minutes.

External examination of the body revealed a facies typical of renal agenesis with a prominent epicanthic fold and large soft ears lacking cartilage, set in a low oblique position. The feet were in a valgus position. The infant was accepted as a male because of a structure thought to be a penis and the absence of labia or vaginal orifice. When the pelvic and abdominal organs were investigated the gonads were found to be ovaries and were adjacent to normal-appearing Fallopian tubes. The lower end of one tube frayed out into surrounding tissues and the other end was attached to a small nodule adjacent to the bladder (Fig. 7). Both kidneys and ureters were absent. The anus was imperforate and the terminal portion

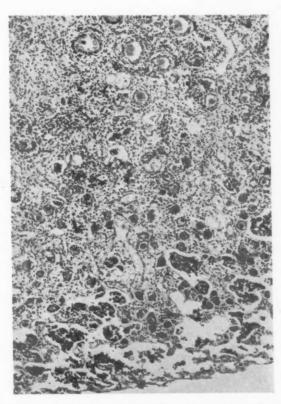


Fig. 4.—Section of normal ovary from infant with penile urethra shown in Figs. 5 and 6 (Case 1). ( $\times 130$ ; reduced  $\frac{1}{2}$ .)

of the sigmoid colon communicated with the bladder. Meconium-stained material could be expressed from the patent urethra. The vagina could not be identified but microscopic examination of a small mass above the bladder revealed several small masses of squamous epithelium with minute central lumina which probably represented an abortive attempt at formation of a vagina.

The penile structure had a central urethra surrounded by erectile tissue typical of the corpus cavernosum urethrae with well, but somewhat irregularly, developed corpera cavernosa penis. The ovaries contained numerous primordial follicles and were normal for a premature fetus. The lungs were extremely hypoplastic and almost no alveoli had developed. Nuclear chromatin was of the female type.

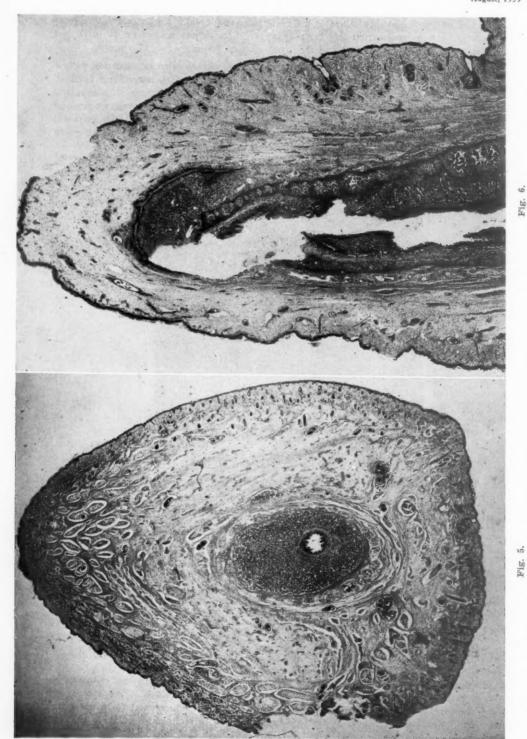


Fig. 5.—Section through proximal end of penile structure showing urethra surrounded by corpus spongiosum. (X10; reduced 4;) (X20; reduced 1/1.)

preputial fold, urethra, corpus spongiosum, and corpus cavernosum, glans, structure showing penile

reduced

Case 3.—51245. A white fetus with a typical sirenomelus deformity (Fig. 1) weighed 1,580 grams and measured 33 cm. in length. No clinical history was available. External examination revealed a facies typical of complete renal agenesis with prominent epicanthic folds and large low-set ears lacking cartilage. Skeletal malformations included absence of the left radius and thumb, absence of one finger of the right hand, extreme hypoplasia and fusion of bones, and soft tissues of lower extremities. Anus and vagina were absent. To the left of the midline on the lower abdominal wall was a structure 2 cm. in length resembling a penis with glans, prepuce, and central urethra and flanked on both sides by small folds, suggesting rudimentary labia or a hypoplastic bifid scrotum. Examination of the body cavities revealed hypoplasia of the lungs, bilateral absence of kidneys and ureters, and absence of bladder, uterus, and vagina. The sigmoid colon and rectum were absent. The ovaries and Fallopian tubes appeared normal. The lower ends of the Fallopian tubes frayed out into suprapubic fat.

Microscopically the tubes and ovaries were normal. The ovaries contained normal primitive germ cells, primordial follicles, and one follicle with luteinization of the theca interna. The nuclei in all sections were of the female type.



Fig. 7.—View showing penile structure, colon terminating in bladder, normal adrenal glands, Fallopian tubes, and ovaries. Uterus absent except for rudiment attached to left tube (Case 2).

Case 4.—42258. A white fetus weighing 1,005 grams, measuring 32 cm. in length was delivered as the first of twins in the first pregnancy of a 22-year-old woman. The first twin was considered male, the second female. The placenta was fused and had 2 amnions and 2 chorions. Both twins were stillborn. The second twin weighed 1,230 grams and was a normally formed female who appeared to have died of intracranial hemorrhage.

The first twin had multiple skeletal malformations including shortening of the ulna and bilateral absence of the radius and thumb producing typical clubhands. The right tibia

and fibula were absent and a six-toed foot was joined at the knee. The left foot was in an equinovalgus position with incomplete separation of the first two toes. The spine was scoliotic producing a concavity of the left chest and convexity of the right. There was no indication of an anus. The external genitals were stated to be rudimentary but were not further described.

The organs in the body cavities were normal except that the colon terminated in a blind pouch in the region of the mid-descending colon, and the kidneys, ureters, and bladder were absent. Testes were stated to be in the abdomen, one attached near the diaphragm. Unfortunately they were not examined microscopically.

This autopsy was performed in another institution and tissues and protocol sent to the Chicago Lying-in Hospital as part of a routine procedure. The fetus was accepted as a male until the present investigation led to the discovery of a female nuclear chromatin pattern. It is very unfortunate that the gonads were not examined microscopically for if they were ovaries this case would be similar to the preceding three cases, while if they were actually testes it would be the first case of Klinefelter's syndrome to be described in a newborn infant.

This case illustrates very graphically, however, the mistakes in designation of sex that can follow superficial and incomplete examinations.

# Sexual Maldevelopment Associated With Other Congenital Abnormalities

Malformations of the sex organs have been described in association with malformations of all kinds in all parts of the body and in some instances investigation of individuals with nongenital abnormalities has contributed a great deal to our knowledge of disturbances in formation of the genital system. In fact, the intelligent observation of sex linkage in certain congenital malformations led to a major discovery in the field of developmental pathology. Whereas the Turner-Albright syndrome of "rudimentary ovaries" associated with infantilism, dwarfism, and other congenital anomalies 19-21 is found almost exclusively in females, coarctation of the aorta occurs predominantly in males, Observing the combination of these conditions in 3 patients assumed to be female, Polani, Hunter, and Lennox<sup>2</sup> investigated their nuclear chromatin pattern and found it to be male. This surprising discovery caused a great sensation but it was soon widely confirmed3, 4, 12 and the majority of patients with the Turner-Albright syndrome have been shown to possess male-type nuclei. The experimental work of Jost<sup>22, 23</sup> showed that sexual development along a female pattern follows early intrauterine castration of male rabbit embryos and it is now generally believed that a similar situation occurs in the human in the Turner-Albright syndrome—that some unknown factor destroys the embryonic male gonad and that this is responsible for development of a female genital tract. The same or a related damaging factor is thought to cause the associated anomalies of other organs generally found in these patients. In related conditions of male pseudohermaphroditism ascribed to a lesser degree of embryonic testicular damage, associated congenital anomalies are also observed.3, 4

Recently, a similar correlation has become apparent in an entirely different condition, Klinefelter's syndrome. This was originally regarded as an endocrinologic and morphologic testicular disorder, accompanied by azoospermia and eventual gynecomastia. In 1956 it was discovered simultaneously by different investigators, 5-8 that a large number of these patients, who present a male habitus and entirely normal male genitals, have female-type nuclei. As a consequence this condition seems to constitute the opposite of the Turner-Albright syndrome in relation to genital development and nuclear sex.

Pasqualini and co-workers<sup>24</sup> in 1957 stressed the high incidence of mental deficiency in patients with Klinefelter's syndrome. This prompted the investigation of nuclear sex in mentally retarded patients by Ferguson-Smith<sup>25</sup>

and by Prader and associates.<sup>26</sup> Both studies led to the discovery of an unsuspected number of patients with chromatin-positive nuclei and a testicular disorder characteristic of Klinefelter's syndrome.

That malformations of the genital organs are frequently found in association with renal agenesis has been recognized by many investigators. 15, 27 This association has been observed not only in dead infants with bilateral absence of the kidneys, but also in patients with less marked or unilateral urologic abnormalities which have not directly interfered with survival. 28-30 The frequency with which urinary tract deformities occur in conjunction with a malformed vagina or uterus is well known to gynecologists. 31-35

From our series and from some of the pertinent literature, the impression is gained that, in the male, malformations of the internal genital organs are less frequent and less pronounced. Definite data as to their real incidence and extent, however, could be provided only by a sufficiently large number of suitable cases studied in detail as was done by Davidson and Ross. <sup>15</sup> As pointed out by Guizetti and Pariset <sup>36</sup> internal genital malformation in adults is considerably more difficult to detect in the male than in the female. Especially careful scrutiny is all the more necessary to exclude such anomalies in male fetuses and newborn infants.

None of the female infants in our series possessed a completely normal genital tract. The least severe malformation was a double uterus with a complete septum and two separate cervices with the remainder of the genital tract normal. Internal genital anomalies in females with bilateral renal agenesis are extremely common and the presence of an entirely normal genital tract in such females must be a very rare occurrence, although such a case was recently described by Duxbury.<sup>37\*</sup>

Absence or malformation of the external genitals has been reported<sup>27</sup> but possible marked or complete masculinization in female subjects seems not to have been widely recognized.

The presence of a major anorectal malformation of the same type in all 4 of our female pseudohermaphrodites with penile urethras is striking. Moreover, the incidence of such anal abnormalities is high in the whole series, being approximately 40 per cent.

Ladd and Gross<sup>38, 39</sup> have proposed a valuable classification for congenital anorectal malformations that has become widely used. In Type I the rectum is constricted a few centimeters above the anal level. In Type II the anus is imperforate, but perineum and rectum are in coaptation, unlike Type III where they are separated by a distance of several centimeters. In Type IV the bowel is interrupted at a level higher than the perineum and consequently is accompanied by a blind anal pouch.

Anorectal abnormalities were present in 20 of the 48 cases in our series. Fifteen resembled Type III except that the malformations were generally more extensive than those described in living patients and both rectum and sigmoid were frequently absent. In some an even larger portion of the colon was missing.

<sup>\*</sup>After this paper had been accepted for publication an infant was born at the Chicago Lying-in Hospital with bilateral renal agenesis but with normal ovaries, Fallopian tubes, uterine corpus, cervix, and vagina.

Twelve of the anorectal malformations occurred in males, 10 of them being Type III and the others Types I and II.

Eight of the anorectal malformations occurred in females, 6 of them being Type III. In the 2 others the anal orifice was abnormally located. In one of them the rectum opened between the labia, while the bladder opened into the rectum—a cloaca-like anomaly that has also been described by Sieber and Klein<sup>40</sup> in two cases of "nonadrenal" female pseudohermaphroditism. In the other the location of the anus was more posterior than normal, probably related to the absence of the sacrum. Two of the Type III anomalies (Cases 1 and 2) were complicated by the presence of a communication between the rectum and bladder, so that meconium could be expressed through the urethra. In another female of the same category there was a communication between the rectum and a closed vaginal pouch which was distended with meconium.

Anorectal malformations were present in our series more often in females than in males; in the former they were found in two thirds of the cases, in the latter in only one third of the cases.

It is remarkable and probably of significance that in 19 of the 20 infants whose external genitals were abnormal an anorectal malformation was present. The only one with a normal anus and rectum was a male with a slight degree of hypospadias, unaccompanied by cryptorchidism. Among the 28 cases without external genital malformation, only one minor anorectal anomaly, a more sacral location of the anus, was found.

Seven infants in the series presented the fused-limb or sirenomelus malformation. Five were definitely male, one was presumably male and only one was female. All had absent or malformed external genitals. All had an extensive Type III abnormality of the lower intestine. In one infant the urethra was absent and the external genitals, although recognizable, were of a strange shape and abnormally located, forming a taillike appendage at the base of the spine.<sup>41</sup> The only reference to such taillike appendages in association with sirenomelus that we have discovered is by Ballantyne<sup>42</sup> who found several such cases in the literature, but in none was there evidence that the true significance of this structure was appreciated.

The correlation between anorectal anomalies and abnormalities of the urinary and the genital system is also evident in the literature. 38, 39, 43-46 Norris and co-workers 47 noted that the anomalies most often associated with an imperforate anus were genitourinary and that this association occurred predominantly in males.

Moore and Lawrence<sup>48, 49</sup> analyzed the clinical features and the correlated anomalies in 120 cases of congenital anorectal malformation. The danger to life of this lesion is apparent from the fact that half of their patients were less than 5 days of age and only 11 per cent were more than 2 years old. Four patients were stated to be of questionable sex but, unfortunately, no further details were given. The over-all incidence of associated abnormalities was 72 per cent but in the cases examined at autopsy this figure rose to 97 per cent. One third of the patients presented malformations of the urinary tract with megaloureter, absence of one kidney, or aplasia of one kidney being the most frequent. One fifth of the female patients had malformation of the internal genital organs. Twelve patients were mentally deficient. Also present were hypospadias, bifid scrotum, rudimentary penis, and complete absence of the external genitals. One cannot but wonder how rewarding a screening of the nuclear sex type in this series would have been.

# Varieties of Female Pseudohermaphroditism

Through the years different classifications have been proposed for the many varieties of sexual maldevelopment, but recently, because of considerable advance in knowledge in this field, they have become more adequate than they were formerly.8, 50-53 In these attempts at classification, however, little attention has been paid to the possible existence of other malformations. This is rather surprising, for when associated malformations are present in one case and not another it seems very probable that there may be a fundamental difference in the causative factors. For this reason it seems to us appropriate, when studying sexual maldevelopment, to make a distinction between the cases with and those without concurrent extragenital anomalies.

Such a distinction has the advantage, especially in female pseudohermaphroditism, of coinciding fairly well with the dividing line between what is known with reasonable certainty and what is not-between cases tending to depend in their etiology upon a single, specific agent and those governed by as yet unrecognized dysontogenetic factors.

Coexisting anomalies may profoundly alter prognosis and management in any given case and consequently an attempt should invariably be made to determine their presence or absence since the findings may be important in making a differential diagnosis.

Because of these observed differences, we propose to attribute the term "specific" to the cases of female pseudohermaphroditism which show a disturbance in the genital system only, and "nonspecific" to those showing additional malformations in other organ systems.

Specific and nonspecific gonadogenital aberrations seem to occur in both sexes, but the distinction is especially clear-cut in female pseudohermaphrodites. Thus it is possible in our present state of knowledge to propose a simple classification of female pseudohermaphroditism, based on etiological and clinical factors (Table II).

#### TABLE II. CLASSIFICATION OF DIFFERENT FORMS OF FEMALE PSEUDOHERMAPHRODITISM

- I. Specific Female Pseudohermaphroditism Without Associated Malformations,-
  - A. Fetal androgenic influence
  - 1. Adrenogenital syndrome
  - B. Maternal androgenic influence
    - 1. Treatment during pregnancy with androgenic or progestogenic compounds ("artificial" or "latrogenic" female pseudohermaphroditism)

      2. Virilizing tumor during pregnancy (arrhenoblastoma)

      3. Functional deviation of steroid metabolism (\*)

  - C. Other forms of specific female pseudohermaphroditism (unapparent fetal or maternal androgenic factors? undetected congenital anomalies?)
- II. Nonspecific Female Pseudohermaphroditism With Associated Malformations.—
  - "Group 2" of Gross and Meeker, "special group" of Jones, cases reported and quoted here, etc.

#### Specific Female Pseudohermaphroditism

In specific female pseudohermaphroditism, according to the definition, there are no accompanying malformations of nongenital organs. At present several etiological subgroups may be distinguished.

The largest and best known subgroup (Table II, I, A) is made up of cases of so-called adrenogenital syndrome, in the study and treatment of which Wilkins and co-workers<sup>21, 54</sup> have made such important advances. In these cases the source of the androgens masculinizing the female fetus is the fetal adrenal gland itself. Clinically there is evidence in these infants of hyper- and dysfunction

of the adrenal gland at birth, resulting in a marked increase in the output of 17ketosteroids and sometimes in a typical disorder, the so-called salt-losing syndrome, which is characterized by a marked loss of salt and water through vomiting, diarrhea, and other pathways. In surviving untreated subjects, early appearance of sexual hair, advanced bone growth, and a stocky muscular build are noted. The adrenal gland is stated to show marked enlargement and to weigh, in the newborn, as much as 8 grams. In microscopic sections the zona reticularis and the zona fascicularis are described as greatly widened. Biochemically, the syndrome is characterized by the inability of the adrenal cortex to achieve certain steps in the biosynthesis of vital glucocorticoids. This results in the accumulation of intermediate androgenic steroids and their metabolites and in an increased ACTH production by the pituitary as the latter is not inhibited by a sufficiently high glucocorticoid blood level. The synthesis of androgenic steroids is thereby even more stimulated and morphologic hyperplasia of the adrenal gland is enhanced. The only known way of breaking this vicious cycle is by the administration of cortisone or a substitute which provides the vitally needed glucocorticoid and inhibits excessive ACTH production by the pituitary. As a rule the results of this therapy are striking. There is considerable evidence to favor the view that the fundamental fault lies in a deficiency of one or more enzymes essential for the biosynthesis of cortisol. 55 This syndrome, which frequently occurs in siblings, may therefore be considered as a specific biochemical anomaly, due to an inborn error of steroid metabolism. 56

None of the infants of our series showed definite gross or microscopic hyperplasia of the adrenals. Their shape was flat and round, as is usual when the kidney is absent<sup>18, 57</sup> (Fig. 2), except in one infant where they were fused in the midline. The size was proportionate to the size of the infant in most cases and their combined weight generally close to 0.25 per cent of the total body weight of the infant. In a very few of the more severely malformed fetuses the adrenals were slightly hypoplastic or moderately enlarged. The zona fascicularis and the zona reticularis were generally well developed but not abnormally widened.

A second subgroup of specific female pseudohermaphroditism is caused by the presence in the maternal blood of abnormal steroids which are responsible for virilization of the female fetus. Several forms of this subgroup may be differentiated according to the origin of these steroids.

In the first form (Table II, I, B, 1) the source of the responsible steroids is exogenous to the maternal organism and provided by the oral or parenteral administration of androgens or progestational agents to the pregnant woman in an attempt to prevent abortion or to provide treatment for some concurrent This form of specific female pseudohermaphroditism may be called "artificial" or even "iatrogenic." Whereas in the beginning only a few isolated observations were reported, the number of cases being published is now increasing at a disquieting rate, especially since the introduction of progestational agents that are effective when given orally and which have been proved to possess marked androgenic properties. Thus far, cases of genital virilization in the female fetus have been reported after the administration during pregnancy of recognized androgens such as intramuscular testosterone, 58-60 oral methyltestosterone, 58, 59, 61-64 intramuscular methylandrostenediol, 65 and of new orally administered progestational compounds such as 17-ethinyltestosterone (synonyms: ethisterone, pregneninolone, anhydrohydroxyprogesterone). 63 17-ethinyl, 19-nortestosterone (synonym: norethisterone), 66 and 17-methyl, 19-nortestosterone (synonym: normethandrolone, methylestrenolone).67

The degree of virilization of the external genitals of the infant is dependent on the androgenic potency of the compound, the dosage and duration of the therapy, and especially on the stage of embryologic development at the time medication is started. In the cases of iatrogenic pseudohermaphroditism so far reported, the only abnormality that has been observed is virilization of the external genitals, and this at times has been extreme. The internal genital organs have been found normal in all instances where an exploratory laparotomy or autopsy was performed. In this variety of pseudohermaphroditism signs of abnormal adrenal secretion are lacking, the 17-ketosteroid excretion is within normal limits, and the clinical course is generally uneventful. Therapy is ordinarily not indicated, except for plastic surgery of the external genitals at a suitable age in the cases of marked masculinization. This unintentional human experiment strikingly demonstrates the sensitivity of the female fetus to circulating androgenic steroids. In contrast, the male fetus, as indicated by the observations of Davis and Potter,68 does not seem to sustain any adverse morphogenic effect on its genital system by the daily administration of high doses of oral diethylstilbestrol or intramuscular testosteronepropionate to the mother in the course of the second trimester. Thus far no complications resulting from administration of any steroids to the mother during pregnancy have been described in the male fetus or newborn.

A second, but evidently very rare, form of specific female pseudohermaphroditism caused by androgens in the maternal circulation is due to the existence of an androgen-producing tumor in the mother during pregnancy (Table II, I, B, 2). A remarkable case was described by Brentnall<sup>99</sup> in which an arrheno-blastoma of the ovary complicated pregnancy. At birth the infant presented a urethral opening at the base of an enlarged clitoris, the labia minora were fused, the labia majora were corrugated and separated by a raphe. Clinical examination disclosed no other congenital abnormality. Another such case was described by Xavier and De Abreu Junquiera, o cited by Javert and Finn. In this instance the virilization of the female fetus was less marked and consisted only of an enlargement of the clitoris, the remainder of the external genitals being normal.

One would be justified in supposing that other virilizing tumors in the mother, such as adrenal adenomas or carcinomas, might equally well masculinize the female fetus. It is possible, however, that the presence of such a tumor interferes with the establishment of a pregnancy and that this is the reason such an association has not been described. The time of onset and rate of tumor growth are probably also important in this respect. Again, it is interesting to note that under such circumstances only the female fetus is affected and the male fetus seems immune to genital malformation. In 3 cases of pregnancy complicated by an arrhenoblastoma, quoted by Javert and Finn, 12 ended with the delivery of normal male infants while the third (of unknown sex) terminated in an abortion.

In this subgroup caused by the influence of maternal androgens, a third form (Table II, I, B, 3) of specific female pseudohermaphroditism, due to a functional deviation of maternal steroid metabolism during pregnancy, might be postulated. Although its existence as an entity still has to be established, rather sparse but somewhat suggestive evidence is available.

Recently, Wilkins and co-workers<sup>63</sup> reported the case of a patient (A-66969) whose picture had been published earlier in his textbook<sup>21</sup> under the heading of nonadrenal female pseudohermaphroditism. But for some interesting features of the maternal history, which subsequently came to light, this case might have been considered a genuine example of female pseudohermaphroditism occurring in the absence of fetal and maternal androgenic influence. The patient was born of a first pregnancy during which the mother, although she received no hormone treatment, had shown a marked increase in weight (74 pounds), a

deepening of the voice, coarsening of the features, and an increased amount of facial hair. After the birth of the patient the mother had had seven pregnancies all associated with some swelling of the face and all ending in miscarriage. Three fetuses were identified as male. In the four others identification of sex was impossible. The ninth pregnancy was unaccompanied by untoward symptoms and resulted in the birth of a normal girl.

In another case of nonadrenal female pseudohermaphroditism (N. H., B34604) reported by Wilkins and co-workers<sup>63</sup> and also by Jones<sup>72</sup> and Jones and Scott,<sup>73</sup> the mother received no hormone treatment during pregnancy, but was troubled with severe acne on the skin of the back, shoulders, and face and thought, herself, that she had some enlargement of the clitoris. Acne and facial

hair disappeared after delivery.

These observations would seem to be of the utmost importance and may occur less rarely than appears to be the case from the few published reports. It is not impossible that in early pregnancy functional disturbances in maternal steroid metabolism may alter the development of the external genitals of an otherwise normal female fetus. At the present time, more data are needed and it would be extremely worth while to investigate history, clinical symptoms, and steroid metabolism of all mothers who have borne a female child with nonadrenal pseudohermaphroditism as well as those who have presented symptoms during pregnancy suggestive of the two cases reported by Wilkins, Jones, and Jones and Scott.

It is interesting that in spite of its widespread use in early pregnancy progesterone has so far been implicated in only a few instances of virilization of the female fetus, 63 Wilkins has postulated that the mothers of these children must differ from others in some unknown way pertaining to the diffusion or metabolization of the administered steroid. This may be equally true for other steroids and in this relation the case of Vandekerckhove<sup>74</sup> is noteworthy. From the beginning of the pregnancy he administered methylandrostenediol orally in increasing amounts so that by the time of delivery a total of 6.85 Gm. had been given. A female infant was born who had normal external genitals. This contrasts with the findings of Zander and Mueller<sup>65</sup> who administered less than half this dose of methylandrostenediol by intramuscular injection twice weekly and started treatment only after the sixth month of pregnancy yet noted marked virilization of the female infant at birth. The explanation of this difference may lie in the mode of administering or in a markedly different sensitivity in the 2 women. In either case it must be assumed the metabolism of the compound was different.

In our series of sexual malformations accompanying renal agenesis the maternal history was irrelevant in practically every case. Hormone treatment was not given and the few recorded abnormalities in the mother before or during pregnancy seemed not to be more frequent than would be expected in a random sample of mothers who bore normal children.

In a last subgroup of specific female pseudohermaphroditism (Table II, I, C) those cases may be placed in which neither a fetal nor a maternal androgenic influence seems responsible for the virilization observed in the infant's external genitals at birth but which, according to the definition "specific," lack associated abnormalities of the extragenital organs. Cases fitting into this subgroup have been described by Chanis, 5 Cotte (2 cases), Jones, 2 Jones and Scott (Patient C. L., A-90431), and Haynes and associates. Unfortunately, prenatal data are lacking in all these cases since 4 of the 5 were adults when first seen. It is to be noted, however, that without the valuable information about the maternal symptoms during pregnancy, the cases of Wilkins (A66969), Jones, 2 and Jones and Scott (N. H., B34604), which have been previously

mentioned, would also have been placed in this subgroup. It is also remarkable how similar the cases of Chanis<sup>75</sup> and Cotte<sup>76</sup> are to Case A66969 of Wilkins. All lacked clinical evidence of adrenal hyperplasia, all had a female habitus and hair distribution, and, most important, all had the spontaneous onset of breast development and menstruation at a normal age. Moreover, the pregnancies subsequent to corrective surgery of the external genitals in both of the patients described by Cotte are striking proof of the normal procreative

possibilities of such women.

It is our feeling that with improvement in clinical investigation the cases in which fetal and maternal androgenic influence as well as associated anomalies are reportedly absent will become more and more exceptional. While temporarily a dumping ground for cases of nonadrenal female pseudohermaphroditism in which essential data relating to maternal history, fetal adrenal, and associated extragenital anomalies are lacking, this subgroup may well disappear. This disappearance would also depend to some extent on an advancement of our knowledge concerning steroid metabolism in mother and fetus during pregnancy. It seems very probable that the production of specific female pseudohermaphroditism is entirely dependent on an androgenic influence, be it from a fetal or a maternal source or from a combination of both.

# Nonspecific Female Pseudohermaphroditism

Under this heading all cases of female pseudohermaphroditism may be included which, in addition to varying degrees of masculinization of the external genitals, show congenital malformations of other organs. The latter most commonly involve the urinary and internal genital system and the lower intestine. Very often, in a given case, two or more of these systems are affected and the viability of the subject will depend on the extent of these malformations. As a result, such abnormalities may be observed in nonsurviving fetuses and infants

even more often than in adult patients.

The cases we have reported with renal agenesis, imperforate anus, and male-type external genitals clearly belong to this category. Since 4 of our female infants, including the originally misdiagnosed male infant with female-type nuclei, presented this kind of anomaly, it is surprising that it has not been noted before. The only similar case we have been able to find in the literature is one described by Leffler.<sup>57</sup> Marked hypertrophy of the clitoris and the absence of a visible vagina suggested male genitals with hypospadias. Both kidneys and ureters were absent. The adrenals were flat oval discs weighing 6.5 grams. Fallopian tubes and cystic ovaries were present but no uterus could be recognized.

As is readily apparent from a study of the current literature, nonspecific female pseudohermaphroditism, though showing a remarkable correlation with bilateral renal agenesis, is by no means confined to it. Various malformations of the urogenital and intestinal tract and of other organ systems may occur in combination with "nonandrogenic" female pseudohermaphroditism. One example is a case described by Siegel swhich, but for the presence of a single hydronephrotic kidney and ureter, had many features in common with our cases. The child died of acute pyelonephritis 21 days after birth and autopsy disclosed a markedly hypertrophied clitoris, a hypospadic urethra, an imperforate and distended vagina, an imperforate anus, a urethrosigmoid fistula, and a uterus didelphys.

Cases characterized by the combination of masculinization of the external genitals and urogenital abnormalities occurring in the absence of a recognized exposure to androgens have been collected by Jones<sup>72</sup> and Jones and Scott<sup>73</sup> into a "special group." Included were an unpublished case reported by

Douglas and a number of cases, reported by Atkinson and Masson<sup>79</sup> (Case 3), by Howard and Hinman<sup>80</sup> (Cases 1 and 2), and by Perloff and associates<sup>81</sup> (Case 2). Most of the affected individuals were seen at a very young age and often a narrow phallie urethra, a urethrovaginal fistula, a grossly distended bladder, and a urine-filled vagina were complicated by life-endangering urinary infection. Kidney and urethral anomalies were frequent but not invariable, and in no instance was there evidence of adrenal hyperplasia or dysfunction. Two additional cases of female pseudohermaphroditism with urinary tract malformations reported by Papadatos and Klein<sup>82</sup> should also be included in this category.

Gross and Meeker<sup>50</sup> studied 75 patients with abnormal sexual development and classified them into 6 different groups, the first 2 being female pseudohermaphrodites. In their Group I were 28 cases of adrenogenital syndrome; in Group II were 9 cases of so-called "nonadrenal female pseudohermaphroditism." The majority of the cases in Group II had malformations of the internal genital organs. In one the left kidney was absent and in 2 the anus was imperforate. None of the 9 patients had adrenal dysfunction, advanced bone

growth, or excessive urinary 17-ketosteroid excretion.

Three similar cases, 2 of them with renal anomalies, were described by Reilly and co-workers<sup>60</sup> and 2 others with a special type of communication between bladder, vagina, and rectum, complicated by urinary infection, were reported by Sieber and Klein.<sup>40</sup>

Wilkins and associates<sup>63</sup> commenting on "nonadrenal" female pseudohermaphrodites, felt that it was impossible to explain all these malformations on a simple hormonal basis and concluded that a study of a possible hormonal etiology would be of most interest in "nonadrenal" cases without congenital anomalies.

The etiological background of nonspecific female pseudohermaphroditism as well as the interrelationship of its different features is still obscure. It is impossible to tell at the present time whether the masculinization of the external genitals is a coincidental and local developmental abnormality or is due to a

general and as yet unrecognized androgenic influence.

That masculinization associated with other malformations cannot be explained by a single maternal factor seems supported by what has been observed in twin pregnancies. In Case 2, reported by Perloff and co-workers, s1 the twin sibling was a normal female. The same is true for our Case 4 where, except for reportedly large adrenal glands, the female twin was entirely normal. However, in another infant in our series (54118 of Table II) presenting a sirenomelus syndrome and partial absence of the genitals, the other twin, a male, also had multiple major malformations, including hypoplastic kidneys and an imperforate anus. He had, however, no genital abnormalities and the cell nuclei were of the male type.

The occurrence in a female of a well-formed penis, with glans, prepuce, corpora cavernosa, corpus spongiosum, and complete phallic urethra, remains poorly understood. Although exact figures cannot be obtained, this feature seems more frequently associated with nonspecific than with specific hermaphroditism. According to Prader<sup>83</sup> it is extremely rare to find a completely penile urethra in the adrenogenital syndrome of the female although two remarkable examples of this have been described by Bentinek and associates<sup>84</sup> and by

Matheson and Ward.85

It is noteworthy that in practically every instance of complete penile urethra in a female, doubt as to sex does not arise immediately after birth and the child is assumed to be a male.

The evidence available from experimental and human embryology indicates that the growth and differentiation of a penis with a central urethra in normal

males and in most female pseudohermaphrodites are governed by androgens. However, in nonspecific female pseudohermaphroditism evidence of androgenic factors has never been obtained. Reilly and co-workers<sup>60</sup> have suggested that the masculinization of the genitals should be considered part of a general effect producing a blighted embryo. This view seems to be supported by the close correlation we have observed between absence or malformation of the external genitals and abnormalities of the internal genital organs and the lower intestinal tract. Nevertheless it is difficult to imagine how the genital tubercle would be stimulated to develop into a near-perfect replica of the male organ by the usual teratologic factors.

Perhaps the lack of more valid arguments in favor of an androgenic influence may be due to the rarity of the syndrome or to the limitations or our investigative procedures. In any case, several possibilities might be considered to account for the observed facts. In order to explain the greater frequency of a complete penile urethra in cases where other internal malformations are present, it seem necessary to assume that the responsible agent must exert an influence earlier in pregnancy than does the fetal adrenal hyperplasia associated with the adrenogenital syndrome. It must then also be assumed that this influence is temporary or has other features preventing its detection at birth. It might have its origin in some as yet undetectable disturbance in the mother or possibly in some intrinsic change in placental structure or function. Whatever the real explanation, the possibility that malformations and disturbances in steroid metabolism may be interrelated or may, in some way, even be related to a common factor, cannot be dismissed.

The 12 cases of nonspecific female pseudohermaphroditism cited by Wilkins together with the ones reported and quoted here make a total of 23. This syndrome, however, is probably not as rare as was formerly thought, although its frequency cannot yet be accurately estimated. If the entire literature on anorectal, genital, and renal malformations were carefully investigated, many more cases of a similar nature would doubtlessly be found. Determination of the sex chromatin pattern in smears or histologic sections from patients with these conditions, would be of the utmost interest. Our study was limited to cases of complete bilateral renal agenesis yet, in this series alone, 4 nonspecific female pseudohermaphrodites were found, one of them not recognized as female until the chromatin pattern was studied. As already stressed, it should be realized that the associated malformations may compromise viability to such an extent that survival is unusual. In relation to the problems considered here this is unimportant, provided the same interest is shown in fetal and neonatal pathology as in living patients. If not, the real incidence of many congenital disturbances will be greatly underestimated.

#### Conclusion

In our present state of knowledge, a sharp distinction can be made between "specific" female pseudohermaphroditism due to a fetal or maternal androgenic influence and not complicated by congenital anomalies, and "nonspecific" female pseudohermaphroditism in which no androgenic influence can be demonstrated but which is accompanied by malformations of other organs. The existence of these two distinct types is doubtless related to the chronology and mechanism of the etiological factors involved.

If we are to learn more about the etiology of sexual malformation in the human, the gonads, genital organs, and nuclear sex should be systematically

studied in every fetus and in every newborn whether alive or dead, whenever congenital malformations are discovered. As is readily apparent from our findings, even the most macerated fetus is worthy of careful investigation.

The desirability of thorough inspection of the perineum in every newborn cannot be overemphasized. The passage of meconium through the urethra in the absence of an anal opening is an indication that a rectovesical fistula is present. It should be kept in mind that in such infants as well as in those with urethrovaginal fistulas, urinary infection is a frequent and dangerous complication. As pointed out by Papadatos and Klein, 2 the differential diagnosis between nonspecific pseudohermaphroditism and adrenogenital syndrome may be difficult. Genital malformation, vomiting, and dehydration occur in both, but in the adrenogenital syndrome associated malformations are lacking. Consequently, when such symptoms are present a careful search must always be made for the possible presence of other malformations. The finding of a complete penile urethra in an individual with female chromatin pattern is highly suggestive of a nonspecific type of female pseudohermaphroditism.

Invariably, the nuclear sex and the urinary, genital, and intestinal tracts should all be investigated as soon as a disturbance in any one of these is observed. No clinical study of a female pseudohermaphrodite should be considered complete without an excretory urogram.

The steroid metabolism and endocrinologic background of any woman presenting signs of virilization during pregnancy or any giving birth to a female pseudohermaphrodite should also be investigated.

# Summary

In view of the frequent association of genital malformations and malformations of certain other organ systems, the discovery of one should invariably lead to an investigation of the possible presence of the other.

Because of the close relationship of the urinary and genital systems in embryologic development and the marked preponderance of males among infants with complete bilateral renal agenesis, genital development and nuclear sex were studied in 48 fetuses and infants presenting this abnormality.

The nuclear sex type was concordant with the external genital sex recorded at birth except in 4 cases which presented a special type of pseudohermaphroditism and were reported in detail. The final result of this study indicated that 13 infants were female, and 35 were male.

The external genitals were often absent, malformed, or, in some females, markedly masculinized. In the female infants the internal genitals were invariably malformed.

Twenty infants in the series presented anorectal malformations, 15 of them having an imperforate anus and an absence of the terminal portion of the intestine. The correlation with external genital malformation was striking.

Seven of the 20 presented a sirenomelus malformation.

A sharp distinction can be drawn between female pseudohermaphroditism with and without associated malformations. For the latter, apparently due to

a single hormonal factor, the term "specific" is suggested, and for the former, apparently having a more complex etiology, the term "nonspecific" is proposed. This terminology has the advantage of stressing important clinical and theoretical differences.

The cases of nonspecific pseudohermaphroditism found in the literature together with the 4 cases reported here make a total of 23. However, the syndrome is probably much more frequent than this would indicate. To appreciate its real incidence and its clinical variations, further study is needed.

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# GAS EMBOLISM: A COMPARATIVE STUDY OF AIR AND CARBON DIOXIDE AS EMBOLIC AGENTS IN THE SYSTEMIC VENOUS SYSTEM

THOMAS D. GRAFF, M.D., NEIL R. ARBEGAST, OTTO C. PHILLIPS, M.D., LEROY C. HARRIS, M.D., AND TODD M. FRAZIER, Sc.M., BALTIMORE, MD.

(From the Anesthesiology Department, The Hospital for the Women of Maryland and the Bureau of Biostatistics, Baltimore City Health Department)

IN 1920 Rubin<sup>17, 18</sup> described a method of determining the patency of the Fallopian tubes by the intrauterine insufflation of oxygen with the production of an artificial pneumoperitoneum. Since that time, the principle of the Rubin test for tubal patency has been universally accepted, although the technique and apparatus originally described have undergone numerous modifications. One of the earliest innovations was the substitution of carbon dioxide for oxygen as the insufflating gas of choice, the reason being that it was more rapidly absorbed from the peritoneal cavity, thus causing less postoperative discomfort to the patient.<sup>19</sup> Subsequently, occasional reports<sup>2, 11, 23</sup> of gas embolism with fatal results following the use of air or oxygen in diagnostic Rubin tests led to a second and more important reason for the use of the more soluble gas, carbon dioxide, as the insufflating agent.

Nevertheless, in spite of the widespread acceptance of the hazards involved, air and oxygen continue to be used commonly for tubal insufflation as well as for diagnostic air contrast studies in the practice of urology and surgery.<sup>1, 7, 8, 16</sup> Based on a survey of 1,267 urologists, Ransom and coworkers<sup>14</sup> reported 58 deaths and 64 severe nonfatal cases of gas embolism resulting from retroperitoneal pneumography. They discovered that air was by far the most commonly used agent and that only two urologists reported using carbon dioxide as a contrast medium. This paper is a report of a comparative study carried out in our laboratory demonstrating the median lethal doses of carbon dioxide and air when injected into the left external jugular vein of the dog.

#### Method

A total of 89 mongrel dogs, weighing between 5.1 and 9.7 kilograms, were used in this experiment. No preanesthetic belladonna drugs were used. Anesthesia consisted of intraperitoneal pentobarbital, 30 mg. per kilogram of body weight, and the animals were kept in the supine position throughout the experiment. On becoming areflexic, endotracheal intubation was performed by direct laryngoscopy with a suitable orotracheal catheter, 100 per cent oxygen was administered, and respirations were controlled with a Bennett

positive-negative phase assistor at a rate between 35 and 40 per minute. Intrapulmonary pressures varied with the size of the animal, ranging between 8 and 10 cm. of water during the positive phase to minus 3 and 4 cm. of water in the negative phase. Tidal exchange was judged adequate by observation of the movements of the thoracic wall, being in all cases in timing with the respirator. A Waters to-and-fro canister filled with high moisture soda lime was utilized for the absorption of endogenous carbon dioxide. A mercury manometer connected through a column of heparin solution to the carotid artery provided a means of monitoring the arterial blood pressure.

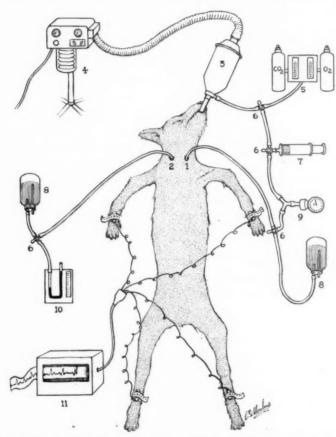


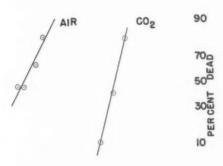
Fig. 1.—Scheme of monitoring and pressure injection system. 1, left external jugular vein; 2, carotid artery; 3, Waters to-and-fro canister; 4, Bennett assistor; 5, Heidbrink anesthesia machine with carbon dioxide and oxygen sources and flow meters; 6, three-way stopcocks; 7, injecting syringe; 8, heparin solution; 9, aneroid manometer; 10, mercury manometer; 11, electrocardiograph.

The left external jugular vein was surgically exposed, and a polyethylene catheter was threaded into the vessel a distance of 2 to 3 cm. and then doubly ligated in place. This catheter provided the means of administering the respective gases, and was connected through a three-way stopcock to a pressure-gauge injecting system as schematically diagrammed in Fig. 1. With this setup it was possible to approximate an injection pressure of 200 mm. Hg, which was used in all cases with both of the gases under study. The time of injection varied with the volume of gas used in each case, ranging between 1

and 3 seconds. A single injection was used in each of the 89 dogs, those surviving being sacrificed at the termination of the experiments, when the vital signs had returned toward normal values. The initial dosage schedule pattern used in this experiment followed the method described by Dixon and Mood,<sup>3</sup> referred to by them as the "Up and Down Method." After this method had been used to provide the dosage range in which some animals lived and others died, intermediate doses were selected.

Electrocardiograms, standard lead II, were taken during each of the experiments just prior to, during, and for 15 seconds following the injection of the gases. Subsequent tracings were made 30 seconds after the injection, and then at 1 minute intervals until the animals either died or tracings similar to those of the control period were obtained. The pulse rate was monitored by analysis of the electrocardiograph at the above-mentioned intervals of time.

# DOSE RESPONSE CURVES AIR AND CO2



AIR: LD50 = 5.1 CC/KG CO2: LD50 = 25.0 CC/KG

#### 3 4 5 6 7 8 9 10 15 20 30 DOSE (CC PER KILOGRAM)

Fig. 2.

## Results

Analyzed by the method of statistical analysis proposed by Litchfield and Fertig, <sup>10</sup> the results of the study are presented in Table I. The dosage points and responses that contribute to the computation of the  $LD_{50}$ 's (lethal dose for 50 per cent of the animals) have been plotted in Fig. 2. Analysis of these data gives an estimate for the  $LD_{50}$  for air as 5.1  $\pm$  0.5 c.c. per kilogram and for carbon dioxide 25.0  $\pm$  1.7 c.c. per kilogram. These  $LD_{50}$ 's are significantly different, and their ratio indicates that air is approximately five times more toxic in its effect than carbon dioxide.

TABLE I. LETHAL DOSAGE FOR DOGS INJECTED WITH AIR AND CARBON DIOXIDE

AIR				1		$CO_2$	
DOSE	NO. OF DOGS			DOSE	NO. 01	F DOGS	
(C.C./KG.)	LIVING	DEAD	% DEAD	(C.C./KG.)	LIVING	DEAD	% DEAD
4.0	5	0	0	9.75	1	0	0
4.5	6	5	45.5	12.2	1	0	0
5.0	6	5	45.5	15.3	1	0	0
6.25	4	7	63.6	19.1	9	1	10.0
7.0	2	9	81.8	23.9	6	4	40.0
7.8	0	4	100.0	29.9	2	9	81.8
				37.5	0	2	100.0
$\mathrm{LD}_{50}$	5.1 ± 0.5 e.e./kg.			$LD_{50}$	6	$25.0 \pm 1.7$	c.c./kg.

#### Comments

The results of this study have demonstrated that in dogs carbon dioxide has a greater margin of safety than does air. From this a reasonable inference might be drawn that the same situation is present in the human. For this reason carbon dioxide rather than air is recommended for diagnostic studies whenever there is the possibility that there might be entrance of the gas into the vascular compartment of the body. These findings substantiate those of Stauffer and associates,<sup>20</sup> who used carbon dioxide as a contrast material for intracardiac roentgenography. They found that intravenously injected carbon dioxide is well tolerated in the anesthetized laboratory animal. These authors later injected 7.5 c.c. per kilogram of body weight intravenously in infants as intracardiac contrast material, and found that the only physiologic dysfunction noted was a transient apnea.<sup>21</sup> A similar response has been noted in dogs where the same dose of air caused a 100 per cent mortality.

It will be noted that the median lethal dose of air determined in this study is somewhat lower than the lethal-dose range reported in other studies. 9, 13, 15, 24 In an attempt to simulate clinical conditions which lead to gas-embolism accidents, we injected our gases at a constant predetermined pressure of 200 mm. Hg. In this way we believe that the rate of injection was better controlled from animal to animal than by simply injecting rapidly or by injecting the different doses in a specified length of time. That this technique is responsible for the smaller median lethal dose for air is suggested by the stress placed on the rate of injection by numerous investigators. Durant, reporting on the efficacy of the left-side-down position in bringing about recovery following the injection of intravenous air, noted not only the importance of the amount of gas used but also the pressure under which the gas was injected. Richardson and his group<sup>15</sup> likewise found that the rate of injection was of great importance. These investigators found that if the rate was less than 1 c.c. per kilogram per minute large quantities could be toler-They described one 23 kilogram animal that received a dose of 1,377 c.c. of air over a period of 460 minutes before dying. Wolffe and Robertson,24 in contrast to others, felt that the speed of injection was of little significance since, no matter how slowly injected, the air would accumulate in the pulmonary artery and its branches and cause death. They felt that the amount of air necessary to produce death was proportional to the size of the pulmonary artery and its branches. They found that the lethal dose for the rabbit was 0.5 c.c. per kilogram of body weight, whereas, for the dog they reported a lethal dose in the range of 15 c.c. per kilogram.

All of the animals in our series showed electrocardiographic changes typical of acute cor pulmonale, consisting of an increase in the amplitude of the P waves and deepening of the S waves. These findings were transient in the animals which lived. Such changes were more prominent in the carbon dioxide group than in the group which received air. Varying degrees of atrioventricular heart block occurred in all of the dogs which eventually died from either of the two types of embolism. Among the animals surviving, transient conduction defects were commonly seen in the carbon dioxide group but only rarely in the dogs which lived following intravenous injection of air.

With the higher doses of either gas, the blood pressure dropped immediately following injection. In the carbon dioxide group this drop was precipitous, reaching minimum readings within 5 to 10 seconds, whereas when air was the embolic agent the pressure took 20 to 30 seconds before reaching similar shock levels. The degree of pressure drop in both groups was in proportion to the amount of gas injected. After varying intervals of hypotension, usually lasting between 1 and 2 minutes, the arterial blood pressure of the animals in the carbon dioxide group which eventually recovered showed a sudden and dramatic climb. Values exceeding the control readings were reached in a period of a few seconds. This was in contrast to the animals which recovered from intravenous air whose blood pressures following the shock interval characteristically took 30 seconds to several minutes to reach pre-embolic values. The dogs that died following the injection of carbon dioxide had immediate and severe falls in mean arterial blood pressure. The animals which exhibited profound shock with barely recordable pressures, but which eventually recovered, however, soon showed minimal changes in vital signs and electrocardiographic tracings from the control tracings.

The results reported here are of interest in the light of the findings of Moore and Braselton, who compared earbon dioxide and air as embolic material injected into the pulmonary vein. Utilizing the cat as their experimental animal these workers found that doses of air exceeding 0.25 e.c. per pound of body weight injected into the pulmonary vein would lead in most cases to a typical coronary death. In contrast, the same authors were unable to produce a stable coronary embolus by using as much as 3 e.c. of carbon dioxide per pound. In all cases, the latter gas was entirely taken up by the blood in 15 to 20 seconds, the heart not being visibly affected. Moore explains the difference in toxicity levels of the two gases as being due to the twenty fold increase in blood solubility of carbon dioxide over air, as well as the ability of the former gas to combine with the alkaline-buffer systems of the blood.

In the present study, death following the intravenous administration of carbon dioxide can most likely be explained from one of three mechanisms or possibly a combination of all three:

- 1. Acute Cardiac Dilatation.—Richardson<sup>15</sup> was the first to note the acute dilatation of the right ventricle and auricle following the intravenous administration of large doses of air. It seems plausible that a similar response would occur after the massive doses of carbon dioxide used in this experiment.
- 2. Impaired Coronary Flow.—The early signs of myocardial ischemia noted on the electrocardiograph following the injection of either air or carbon dioxide would indicate that the coronary flow is markedly impaired. Oppenheimer, Durant, and Lynch,<sup>13</sup> studying the cardiovascular changes in air embolism, have shown a biphasic elevation of the pulmonary arterial blood pressure concomitant with the fall in systemic arterial pressure. Observing a localized right ventricular ischemia in a series of open-chest experiments, these same authors,<sup>4, 5</sup> in explaining the phenomenon, cited the work of Visscher,<sup>22</sup> who demonstrated the importance of the pressure gradient between the aorta and the pulmonary artery in maintaining coronary blood flow.
- 3. Anoxia.—The large bolus of carbon dioxide injected into the systemic venous system lodges in the pulmonary arterial bed; effective pulmonary circulation ceases. This results in marked impairment of the gas exchange normally carried out between the alveoli and the pulmonary capillaries.

An appreciation of the amount of intravenously injected carbon dioxide necessary to bring about the death of the experimental animal is apparent when one remembers that the average 6 kilogram dog has a blood volume of about 500 c.c. The median lethal dose amounts to 30 per cent of this volume. If such results can be carried over to the human, the LD<sub>50</sub> of intravenous carbon dioxide in a 50 kilogram person would amount to values of 1,200 to 1,300 c.c. It is unlikely that such volumes of carbon dioxide are ever used clinically with the possible exception of the Rubin test. It is common practice in many gynecologic clinics to bring the insufflating pressure repeatedly to 150 to 200 mm. Hg, in an attempt either to open nonpatent Fallopian tubes, or to investigate the possibility of a leak in the Rubin apparatus. When such a practice is carried out, it seems advisable to allow intervals of several minutes to elapse between insufflations while observing the blood pressure closely for any indications of instability.

# Summary

The median lethal doses of intravenous air and carbon dioxide were determined in 89 mongrel dogs. This study showed that air is approximately five times as toxic as carbon dioxide as an intravenous embolic agent. Blood pressure and electrocardiographic changes are described and possible mechanisms of death are discussed. The relative toxicity differential between the two gases in laboratory animals is offered as evidence for the preferential use of carbon dioxide as an insufflating or gas contrast material in clinical practice.

We wish to express our gratitude to Dr. J. Frank Supplee, III, for his invaluable assistance in interpreting the electrocardiographic tracings.

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### THE ROLE OF CULDOSCOPY IN INFERTILITY\*

MELVIN R. COHEN, M.D., CHICAGO, ILL.

(From the Division of Obstetrics and Gynecology, Michael Reese Hospital)

CULDOSCOPY, or transvaginal peritoneoscopy, permits direct observation of the female internal organs of reproduction. The procedure was developed by Decker<sup>1</sup> in 1943 and his instrument is the one utilized. This operation was performed on 458 patients in the past 8 years; 316 of these women complained of infertility. This is a report of the findings in the entire series, but particular emphasis is placed on the infertile group.

When first utilized at Michael Reese Hospital, the procedure was instituted for evaluation as a diagnostic method in gynecology. Patients with unexplained pelvic pain, especially when there was some suspicion of an ectopic pregnancy, were selected for differential diagnosis by this technique. Subsequently, the use of this diagnostic method was extended to eases of amenorrhea and menometrorrhagia in order to observe the ovaries in such conditions. At the present time our chief indication for culdoscopy is in the complete survey of the infertile female.

On Dec. 16, 1949, Teton<sup>2</sup> presented a paper before the Chicago Gynecological Society entitled "Diagnostic Culdoscopy," based upon his experience in 96 cases. His enthusiasm for this diagnostic procedure apparently has not been shared by other members of this Society, as there have been no further papers on this subject until now.

Since 1944, there have been numerous reports about culdoscopy in the American literature and about Douglasscopy in the Latin American and European literature.<sup>3-13</sup> The consensus of these reports is: (1) culdoscopy is a simple operative procedure; (2) it is relatively safe in the properly selected patient; (3) complications are rare but are more frequent with the inexperienced operator; and (4) it is invaluable in obscure pelvic pathology, especially in the differential diagnosis of acute disorders, for example, ectopic pregnancy.

There are definite contraindications to this procedure, the principal one being the inability to demonstrate a free cul-de-sac. Culdoscopy should not be attempted when the uterus is in fixed retroversion, when there is a mass in the cul-de-sac, when there has been extensive pelvic surgery, or when extensive vaginal disease precludes the possibility of instrumentation. Also, the procedure is contraindicated when there would be cardiac or respiratory embarrassment in the knee-chest position and in cases of surgical shock.

<sup>\*</sup>Presented before the Chicago Gynecological Society, Nov. 15, 1957.

The technique of culdoscopy has been well documented by Decker.<sup>1</sup> Our presently employed procedure includes two slight modifications as follows:

- 1. Positioning of patient in a fixed attitude.
  - a. The patient is "jackknifed" in knee-chest position with the knees resting on a rubber-padded footboard, approximately 12 cm. below the level of the operating room table. (Fig. 1.)
  - b. Shoulder braces maintain the patient in this position.
  - c. The position is laterally stabilized with the aid of upright stirrups which support the thighs and hips.
  - d. A wide canvas strap across the patient's back creates an exaggerated lordosis.
- 2. Creation of a minimal pneumoperitoneum prior to the introduction of the trocar.
  - a. The cul-de-sac is identified and infiltrated with local anesthesia. An 18 gauge spinal needle attached to a 10 c.c. syringe with the barrel removed is inserted through the cul-de-sac. When a free cul-de-sac is identified, air will be heard rushing in. Following this added procedure, the cannula with trocar is more safely introduced.



Fig. 1.—Positioning of patient for culdoscopy.

#### Culdoscopy Findings

Culdoscopy was performed in 458 patients (Table I), in the past 8 years; 316 of these women complained of infertility. The summary of findings in the infertile group are shown in Table II. A preoperative diagnosis of ectopic pregnancy was made in 69 cases (Table III). Tubal pregnancy was demonstrated in 20 patients and confirmed at laparotomy. Of the group of amenorrheic women (Table IV) 17 were single and 24 complained of infertility. There were 29 patients who complained of menometrorrhagia (Table V). In all of these 29 patients, dilatation and curettage was performed at the conclusion of the culdoscopy. Pelvic pain which could not be accounted for by physical examination was the presenting complaint of 17 patients (Table VI).

TABLE I. INDICATIONS FOR CULDOSCOPY\*

Infertility	316
Suspected ectopic pregnancy	69
Amenorrheat	43
Menometrorrhagia as corollary to curettage	29
Pelvic pain	17

\*Culdoscopy failed in 8 patients.

†Twenty-four patients complained of infertility.

TABLE II. FINDINGS IN 316 INFERTILITY PATIENTS

Culdoscopy Findings.—		
Recent ovulation*	144	
Adhesions (peritubal and periovarian)	78	
Simple cysts of ovaries	56	
Fibroids	35	
Endometriosis	35	
Bilateral polycystic ovaries	23	
Hypoplastic genitals	16	
Ovarian tumors	4	
Bicornuate uteri	3	
Sclerotic ovaries	2	
Tuberculosis	1	
Pregnancy	1	
Indigo Carmine Tubal Patency Tests		
No. of tests	54	
Positive tests	44	

\*Double corpora hemorrhagica in one patient.

TABLE III. CULDOSCOPIC FINDINGS IN 69 PATIENTS WITH SUSPECTED ECTOPIC PREGNANCY

Proved tubal pregnancy	20
Pelvic inflammatory disease	15
Normal status	9
Intrauterine pregnancy	7
Incomplete abortion	7
Ovarian cysts	5
Endometriosis	2
Ruptured Graafian follicle	2
Bilateral polycystic ovaries	1
Ovarian pregnancy	1

TABLE IV. CULDOSCOPIC FINDINGS IN 41 PATIENTS WITH AMENORRHEA\*

Hypoplasia	9	
Bilateral polycystic ovaries	9	
Follicle cysts	6	
Ovarian agenesis	5	
Normal status	5	
Pelvic inflammatory disease	2	
Corpora hemorrhagica	2	
Small bilateral polycystic ovaries		
(adrenogenital syndrome)	2	
Luteoma	1	
Pregnancy	1	
Postoperative adhesions	1	

\*Associated with infertility in 24 cases; in single women, 17 cases.

# Complications

Complications occurred in 10 of the 458 patients in whom culdoscopy was performed in 8 years, an incidence of 2.2 per cent. These complications consisted of:

1. Paresthesia of the upper extremities which was attributed to the pressure of shoulder braces. The paresthesia was mild and transient.

2. Bleeding from the vaginal puncture which required only a single

suture. This occurred in 2 patients.

- 3. Postculdoscopy fever, probably due to acute pelvic inflammatory disease. This patient not only made a complete recovery but subsequently became pregnant and delivered at term.
  - 4. Acute pelvic inflammatory disease with residual unilateral adnexitis.
- 5. Late hemorrhage from a sloughing area in the cervix traumatized by the tenaculum forceps.

6. Pneumomediastinum.

7. Subcutaneous emphysema in the clavicular areas.

8. Fatal pulmonary embolism in early pregnancy, 7 days following culdoscopy. (This patient had complained of severe pelvic pain which was the indication for the culdoscopy.) At the time of the postmortem examination, the culdoscopy wound had healed completely and the origin of the clot was not ascertained.

9. Rectal trauma with transient bloody stool.

TABLE V. CULDOSCOPIC FINDINGS IN 29 PATIENTS WITH MENOMETRORRHAGIA\*

Normal status	13	
Chronic pelvic inflammatory disease	9	
Endometriosis	3	
Bilateral polycystic ovaries	3	
Fibroids	3	
Ovarian cysts	2	
Incomplete abortion	2	

\*Dilatation and curettage was performed in all patients after culdoscopy.

TABLE VI. CULDOSCOPIC FINDINGS IN 17 PATIENTS WITH PELVIC PAIN

 Normal status	6
Endometriosis	6
Pelvic inflammatory disease	5
Follicle cyst	1
Broad ligament varicosities	1

# Culdoscopy in Infertility

Culdoscopy has become a valuable addition to our diagnostic armamentarium in the survey of the infertile couple. It has been possible to demonstrate ovulation or failure of ovulation. The routine, indirect observations utilized for the diagnosis of ovulation require the correlation of basal body temperatures, quantity of cervical mucus, spinnbarkeit,14 and the degree of cornification shown on daily vaginal smears. Fig. 2 demonstrates the correlation of these factors in the establishment of ovulation time. In the illustrated typical basal body temperature chart, utilizing rectal temperatures, one may note that the low point in the curve was on day 11. The temperature was then elevated and sustained from day 14 until day 28 with menses beginning on day 29. Profuse mucorrhea occurred on days 11, 12, and 13. During these days the vaginal smear progressed from moderate estrogen effect to full cornification. Postcoital examination (Sims-Huhner test) was positive. On day 14 the cervical mucus became thicker and less profuse. Spinnbarkeit length was only 1 cm. and white blood cells began to appear. The Fern reaction was atypical (+/-). Culdoscopy performed on day 16 demonstrated a normal status with a corpus hemorrhagieum.

The intensely red corpus hemorrhagicum which normally occupies approximately ½ to ½ of the entire ovary can be visualized easily. It is sometimes covered by a substance which has the appearance of clotted blood. At other times there is a tiny transparent membrane through which is seen a dark, purplish liquid center, the "eye" of the corpus hemorrhagicum. In our 316 culdoscopic examinations performed expressly to determine whether or not ovulation had occurred, that phenomenon was clearly demonstrated 144

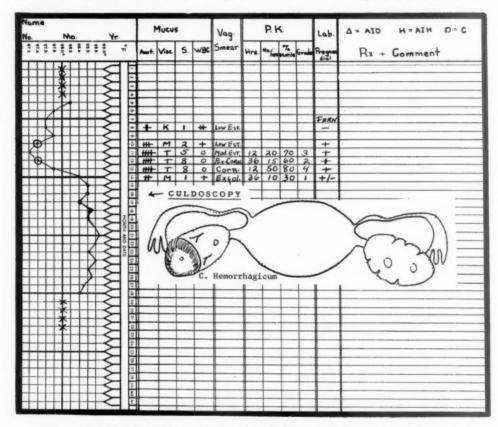


Fig. 2.—Presumptive evidence of ovulation verified at culdoscopy. (Under mucus, Amtrefers to amount of endocervical mucus and is designated from 1 to 4 plus profuse; Visc. refers to viscosity which is designated K as thick, M as moderate, and T as thin; S refers to spinn-barkeit and is measured in centimeters; WBC refers to white cells and is designated as either number per high-power field or from 1 to 4 plus. P.K. refers to the postcoital test. Hrs. means the number of hours after intercourse; No./HPF indicates the number of spermatozoa per high-power field; % Motile, the per cent of these motile; and Grade, their motility designated from zero, no motility, to Grade 4, very active forward progression. Under Lab., reference is made to any laboratory procedure such as the Fern reaction, pregnanediol, or other laboratory tests.)

times. At the conclusion of the test, endometrial biopsy was performed in many instances and the results of endometrial response were correlated with the appearance of the ovary.

The best evidence of ovulation is pregnancy. Ovulation may occur without a typical diphasic basal body temperature curve, cervical mucorrhea and spinnbarkeit, vaginal smear cornification and exfoliation, or typical secretory endometrium. Culdoscopy is invaluable when the above presumptive criteria of ovulation are atypical or absent.

Peritubal and periovarian adhesions were observed in 78 of 316 infertility patients. Such adhesions could be extensive enough to interfere with tubal function and still permit tubal patency to gas (Rubin test) or opaque media. More striking in appearance and more significant were periovarian adhesions which interfered with the extrusion of the ovum from the surface of the ovary.

Small fibroids and many cases of early, silent endometriosis may be observed. The purplish implants, so typical of endometriosis, are clearly demonstrated by this technique; short of exploratory laparotomy, this diagnosis cannot otherwise be made.

Culdoscopy is invaluable in diagnosing the Stein-Leventhal syndrome. By this means, the typical, smooth, large, globular ovaries containing multiple small follicles can be demonstrated clearly.

In the management of the infertile couple, culdoscopy is usually a final procedure, useful in ruling out obscure pelvic pathology. Certainly for those women who have undergone an otherwise exhaustive survey, culdoscopy can be of paramount importance in determining whether they should continue having treatment, institute adoption proceedings, or reconcile themselves to a childless marriage. In the older age group, culdoscopy may be used as a means of a very rapid survey in order to conserve time. Frequently a final prognosis can be given following this examination.

# Summary and Conclusions

During the past 8 years, 458 culdoscopic examinations were performed. Of these, 316 were for the complete survey of the infertile woman. Additional indications were suspected ectopic pregnancy, amenorrhea, menometrorrhagia, and unexplained pelvic pain.

Two modifications of the established technique of culdoscopy are described: (1) the positioning of the patient, and (2) the creation of a minimal pneumoperitoneum prior to the insertion of the trocar.

This diagnostic technique is of great value in cases of longstanding infertility, not only for complete evaluation of the pelvic status, but also because of its aid in prognosis.

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#### Discussion

DR. JOSEPH B. TETON, Chicago, Ill.—Several years ago I received a questionnaire from Professor Thomsen of Germany requesting detailed information on our experience 272

with the culdoscope. Subsequently, I received a reprint from him in which he reviewed almost 5,000 cases that he had collected. I cite this study because in the 5,000 cases reviewed there was not even one serious complication reported.

Dr. Cohen's presentation serves to illustrate the wealth of additional information made available by the culdoscope in the study of the infertility patient. The patient with unexplained infertility presents a special problem which the culdoscope can frequently solve, with respect to finding the cause. In an analysis of the patients who underwent culdoscopy in the last 2 years, in whom infertility was the primary indication, we found a causative factor or factors in about 50 per cent.

Dr. Cohen's almost perfect record of successful punctures—only 8 failures in 458 patients—is a bright example of the nearly uniform success one may expect after familiarizing oneself with the technique.

The accuracy of this procedure in the differential diagnosis of ectopic pregnancy is unique. In some patients, even though all the pelvic organs may not be clearly seen, we have invariably found pathognomonic signs.

Dr. Cohen wondered why more gynecologists have not become interested in the culdoscope. His presentation will help to replace some archaic beliefs about the culdoscope. Others among us may revise or alter our thinking and, with this newly acquired perspective, become enthusiastic culdoscopists.

DR. FRED O. PRIEST, Chicago, Ill.—I have had no personal experience with culdoscopy. I feel sure that I should have had, particularly in regard to its use in the treatment of sterility.

I should like to ask Dr. Cohen if he uses a special lens, such as the oblique or retrograde lens, for inspection of the anterior wall of the uterus and the anterior cul-desac.

In regard to the diagnosis of endometriosis by culdoscopy, with the exception of isolated small transplants on an ovary without fixation, I believe that in most cases we should be able to make the diagnosis by bimanual examination. Endometriosis without some cul-de-sac involvement is rare, and even quite small areas in the true pelvis should be diagnosed after repeated rectovaginal examinations with the rectum thoroughly empty.

We would still prefer colpotomy over culdoscopy for ectopic pregnancy before shock symptoms. Drs. Draa and Baum reported to this Society 149 such cases proved at colpotomy. In 77 of these, or over 51 per cent, the pregnancy was removed through the colpotomy incision. After shock symptoms appear neither colpotomy nor culdoscopy has a place in the treatment.

DR. ERNEST M. SOLOMON, Highland Park, Ill.—We have been using the culdoscope for the past 4 years but not in the routine systematized fashion of Dr. Cohen. In our hands, its use has been restricted to patients with infertility and those with dysmenorrhea in whom we were trying to prove or disprove the presumptive diagnosis of endometriosis and those patients suspected of having an unruptured ectopic pregnancy in whom the index of suspicion was not high. With a high index of suspicion we use colpotomy since we prefer to remove the intact tubal pregnancy by the vaginal route.

We agree with Dr. Cohen that the procedure is simple and easily performed. After initially using saddle block or pudendal anesthesia which makes the procedure cumbersome, we now routinely use local infiltration. In some 30 cases we have had no complications. We have confirmed the diagnosis of endometriosis 9 times; found no visible pathologic condition 10 times; and found ectopic pregnancy 10 times. In one most interesting case a purulent pelvic appendix fell into view immediately.

More recently we have tended to favor colpotomy as the diagnostic procedure of choice as being, in our hands, more satisfactory. I am sure, however, that in Dr. Cohen's hands, because of his large experience in visual interpretation of a lens-transmitted view,

the culdoscope is equally valuable. I believe that if doctors generally were aware, as Dr. Cohen is trying to make them, of the safety and simplicity of the procedure it would be used more and more, with a proportionate increase in valuable experience.

Perhaps by the time Dr. Cohen has studied another 300 infertility patients his correlation of the visual findings with other diagnostic criteria of ovulation will make the procedure unnecessary in the determination of ovulation.

DR. COHEN (Closing).—Both Dr. Priest and Dr. Solomon mentioned colpotomy. Any diagnostic procedure is good if you get a good result. Colpotomy as performed by the Presbyterian group, by Dr. Solomon, and by Dr. Lash is a nice procedure, but culdoscopy is another procedure which is very simple and easy to become familiar with.

To answer Dr. Priest, most of our cases were performed with the Decker lens which is not a fore-oblique lens. You can see practically everything in the pelvis except the structure adjacent to the culdoscope and pathologic conditions along the uterosacral ligaments.

Concerning endometriosis, Dr. Priest made the statement that it is rarely present without masses in the cul-de-sac but we have found this condition to be amazingly frequent without symptoms.

# STERILITY DUE TO RETROGRADE EJACULATION OF SEMEN\*

# Report of Pregnancy Achieved by Autoinsemination

Donald Walters, M.D., and Morton S. Kaufman, M.D., Washington, D. C.

(From the Department of Obstetrics and Gynecology, George Washington University Hospital)

RETROGRADE ejaculation may be caused by inflammation, trauma, or congenital malfunction of the posterior urethra. It practically always follows transurethral resection of the prostate; traumatic treatments of prostatic infections may also be a contributing factor.<sup>1</sup>

Mrs. M. H., a 30-year-old, gravida 0, white woman, was first seen Dec. 11, 1956. The past history was essentially negative. The general and pelvic examinations were normal at this time. The menstrual flow was irregular, occurring every 5 to 6 weeks. She had been married for 3 years, and had used contraception until March, 1956.

In March, 1956, her husband, aged 50, had a transurethral median bar prostatic resection. Following this procedure he had retrograde ejaculations. The internal urinary sphincter was so disrupted following this operation that the semen at ejaculation entered the bladder instead of being delivered through the penile urethra. The husband was disturbed because he had been assured there would be no change in his "sex life." (The importance of making certain the physician and patient understand each other cannot be stressed too strongly; the husband's question referred to sexual potency and the physician's answer referred to sexual pleasure.) The couple insisted on artificial insemination using the husband's sperm.

Mrs. M. H. was given a complete examination for infertility. The basal metabolic rate was minus 5. An endometrial biopsy produced a secretory endometrium. The Fallopian tubes were patent on insufflation. The blood count was normal. X-ray examination revealed normal lung findings. The blood was type B, Rh positive. The Wassermann test and urinalysis were negative. The basal temperature charts confirmed our inability to determine when ovulation would occur as the temperature rise was variable.

Sperm were obtained by having the husband urinate after masturbation. Centrifuging the specimen produced many nonmotile sperm. The urine was strongly acid. The acidity was not sufficiently controlled by the administration of soda bicarbonate, 5 grains t.i.d., to obtain uniformly good sperm. If the specimen was obtained 2 hours after the ingestion of one dram of soda bicarbonate the motility was poor. The urologist had the husband void and then a catheter was inserted to measure residual and to empty the bladder of all urine. The bladder was then washed with Ringer's solution, one-half ounce of which was allowed to remain in the bladder. Following masturbation and retrograde ejaculation the semen and Ringer's solution were voided but the specimen was not centrifuged since we believed this might injure the sperm. The specimen was allowed to stand for a few

<sup>\*</sup>Presented at a meeting of the Washington Gynecological Society, Washington, D. C., Jan. 28, 1959.

minutes and after this time 4 or 5 c.c. of sediment contained the sperm. The specimens of sperm were good. This was done in June, July, and August, 1957, with attempts at artificial insemination made using the cervical cap method.

The wife was placed on thyroid and cyclic estrogen and progesterone therapy. She was given Premarin, 1.25 mg. daily, for 22 days. She was given progesterone Lingusorbs, 25 mg. b.i.d., for 6 days starting with the sixteenth day of the cycle. This was done for 2 months with bleeding occurring 3 days after completion of medication. It was hoped that the menstrual flow would continue in a regular pattern after completion of cyclic therapy.

In October artificial insemination was done on the fourteenth and sixteenth days of the cycle as outlined. The last menstrual period was Oct. 10, 1957. An Aschheim-Zondek test on Nov. 26, 1957, was positive.

Therefore, after completion of cyclic therapy, ovulation occurred on the fourteenth to the sixteenth day and pregnancy resulted from insemination. The patient, I am convinced, is extremely honest and sincere. She assured me that no other means were used to aid the pregnancy.

The pregnancy was uneventful. The weight gain was 24 pounds; blood pressure and urine remained normal. The estimated date of confinement was July 17, 1958. On Aug. 8, 1958, she was delivered of a 7 pound, 5½ ounce girl. This was accomplished by a Scanzoni maneuver from a right occipitoposterior to a right occipitoanterior position after 14 hours of labor, over a right mediolateral episiotomy.

# Summary

This is the second case report of a successful autoinsemination with material obtained from the urinary bladder, following retrograde ejaculation.

Repeated inseminations during the ovulatory phase with as concentrated a specimen as is possible seem necessary.

Since acids are spermatocidal, the fluid into which sperm are ejaculated must be made alkaline.

In this patient the transurethral prostatectomy was the probable cause of the retrograde ejaculation.

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# INFERTILITY IN FEMALE GUINEA PIGS INDUCED BY INJECTION OF HOMOLOGOUS SPERM\*

SEYMOUR KATSH, PH.D., DENVER, COLO.

(From the Department of Pharmacology, University of Colorado Medical Center)

HAVING reported a possible immunologic method of inducing infertility in female guinea pigs by injections of homologous sperm or testis,<sup>1, 2</sup> it was necessary to examine this suggestion experimentally. This report describes the success obtained.

#### Materials and Methods

Since breeding experiments require elaborate animal care, considerable attention was paid to the care and maintenance of the animals. The diet consisted of guinea pig chow fortified with ascorbic acid and supplemented with fresh greens, carrots, and apples. Drinking water and food were available ad libitum. The animals were kept in well-ventilated, well-illuminated quarters and overcrowding was prevented by keeping not more than 3 females to a cage 3 feet long by 2 feet wide. A total of 63 young adult females (600 to 700 grams body weight) of various coat colors and of proved fertility (following previous timed matings) were treated as noted in Table I. Each injected animal received 3 injections of the respective material on alternate weeks before exposure to the males. One month after the last injection, a single male was placed with each group of 3 females for 7 days and then the males were rotated among the cages. Records were kept of the mating times and the females were examined for copulation plugs as evidence of successful mating.

Guinea pig sperm was obtained and prepared essentially as described previously.<sup>1, 2, 3</sup> Briefly, by means of a 24 gauge needle and a 2 ml. syringe, a 0.9 per cent NaCl solution was forced through the severed end of the dissected vas deferens of exsanguinated male guinea pigs. When the tubules of the epididymis (separated from the testis) became turgid, a slit in the epididymis was made and the sperm was flushed into test tubes. Sperm from many guinea pigs of various coat colors was pooled in order to obtain a wide spectrum of antigenic diversity in consideration of the genetic heterogeneity of the animals used. The pooled sperm suspensions were centrifuged at 2,000 r.p.m. for 10 minutes and the sediment was weighed on a torsion balance. The sediment was resuspended in 0.9 per cent saline, 70 mg. per milliliter. The suspension was then incorporated into an equal volume of Freund's complete adjuvant.<sup>1-3</sup> Rabbit and bull sperm was also obtained and prepared in this manner.

As shown in Table I, 9 females were not injected, 9 were injected with adjuvant emulsified with an equal volume of saline, 9 were injected with guinea pig sperm in adjuvant, 9 received rabbit sperm in adjuvant, and 9 received bull sperm in adjuvant. In other experiments, homologous and heterologous sperm in saline, rather than adjuvant, was injected (Table I). The injections were made intracutaneously at 5 to 7 sites in the nuchal region and each animal received 1 ml. of the respective preparation at each of the injection periods.

<sup>\*</sup>This study was supported by funds from The Population Council, Inc., New York, N. Y.

The experiments were terminated at 320 days counting from the day the females were first exposed to males (1 month following the last injection). Litter data (i.e., date of delivery and number per litter) as well as observations regarding the presence of copulation plugs were recorded.

## Results

The data summarized in Table I indicate that fertility in female guinea pigs was significantly inhibited by injections of homologous sperm in adjuvant.

TABLE I. THE EFFECTS OF INJECTION OF SPERM ON FERTILITY OF FEMALE GUINEA PIGS

NO. OF ANIMALS	MATERIAL INJECTED (35 Mg. SPERM PER INJECTION)	NO. OF ANIMALS THAT LITTERED	LITTER DAY*
9	None	9	67-75
9	Freund adjuvant and saline	8	68-100
9	Guinea pig sperm in adjuvant	2	180,310
9	Rabbit sperm in adjuvant	7	65-111
9	Bull sperm in adjuvant	8	70-103
6	Guinea pig sperm in saline	5	123-170
6	Rabbit sperm in saline	6	70-82
6	Bull sperm in saline	6	75-90

 $^{*}$ Counting from the first day when exposed to a male (one month after the last of 3 injections).

Only, 2 of 9 such animals produced offspring during the 320 days of the experimental period (about 4 gestational cycles in the guinea pig); moreover, these 2 litters were delivered a considerable time after the females were exposed to males, indicating a delay in conception. No other experimental group experienced such a significant decrease in percentage of fertile matings, although a delay in conception was noted in those animals which received homologous sperm in saline. These results correspond favorably with those noted previously in connection with the higher degree of sensitization of the uteri of guinea pigs injected with homologous sperm in adjuvant than of the uteri of guinea pigs injected with homologous sperm in saline. A slight percentage of inhibition of fertility in the other injected animals may be attributed in part to the injections themselves which, with adjuvant, cause a focal area of necrobiosis in the skin of the back thus, perhaps, making mounting by the male an uncomfortable experience for the female. The presence of copulation plugs in the vaginas of the females receiving the homologous sperm in adjuvant rules out the possibility that these animals did not mate. Also the degree of insult to the skin was the same for all animals receiving adjuvant and, thus, the results obtained with homologous sperm cannot be attributed to the injection lesion per se.

#### Comment

Since 1899-1900<sup>4-6</sup> sperm has been known to be antigenic. During the intervening years many attempts have been made to utilize this knowledge to inhibit fertility experimentally in animals and in humans with little, if any, success.<sup>7</sup> Newer approaches in immunology designed to elevate antibody response demanded a re-examination of this approach to infertility. Recently it has been shown that sperm injections can cause sensitization of guinea pig uteri as well as of the ileum of females and males, and that the sensitization is increased if the sperm or testicular tissue is injected with Freund's adjuvant.<sup>1-3, 8</sup> This information, together with the previous evidence that injections of sperm in saline can elicit circulating antibody response,<sup>4-6</sup> made it possible to postulate that infertility might be conferred due to sperm immobilizing, sperm agglutinating, and sperm cytolyzing antibody and by local

uterine anaphylactic response which might inhibit implantation of the blastocyst. The current results indicate that whatever the mechanism(s), some success has been achieved in inhibiting fertility.

These results are presented at this time (with full recognition given to the considerable amount of work yet to be done for further exploration) because of the publication by Isojima and associates wherein it is reported that sterility was induced in female guinea pigs injected with guinea pig testis in adjuvant. Their report confirms our previous findings with guinea pig testis.10 In other experiments, for example, homologous seminal vesicle and prostate in adjuvant had no effect on fertility in female or male guinea pigs injected with such material, whereas homologous brain and ovary as well as testis did inhibit fertility in female guinea pigs.11 It is important to note that the guinea pig is the responsive test animal in the successes achieved; other species have not been so uniformly affected.<sup>11</sup> This bespeaks an immunologic sensitivity

of the guinea pig.

One of the reasons for the presentation of these results at this time is a statement in the paper of Isojima: "There are two possible mechanisms of sterility: 1. cellular immunity, as in Freund's experiment in aspermatogenesis, and 2. circulating antibodies which could appear in the vaginal fluid according to our observations or which could cause the uterus to contract on contact with sperm, according to Katsh." Aside from the stringent limitation on the number of mechanisms of sterility, there is an erroneous (albeit, inadvertent) allusion to the results described in Katsh's paper. It should not be inferred that I excluded sperm immobilization and agglutination (or, indeed, cytolysis) by antibody in attempting to emphasize uterine anaphylaxis. (We have also recorded observations on agglutination and immobilization of sperm by serological antibody. 12) But more importantly the linking of circulating antibody with uterine anaphylaxis should not have been gleaned from the reference cited since no statement to this effect was made. Considerable effort has been expanded in indicating, rather, that with adjuvant an altered state of hypersensitivity probably concerning fixed antibody is involved.<sup>2, 3, 13</sup> With the concept of fixed antibody it is possible to explain the lack of correlation between circulating antibody titer and infertility that Henle and Henle,14 among others, have described. 1-3, 7, 8, 12, 13, 15

# Summary

Female guinea pigs of proved fertility were injected with homologous and heterologous sperm with or without adjuvant. A significant reduction in fertility was observed in those guinea pigs injected with guinea pig sperm in adjuvant.

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# THE QUANTITY OF VAGINAL FLUID

ABRAHAM STONE, M.D., AND CLARENCE J. GAMBLE, M.D., NEW YORK, N. Y.

(From the Margaret Sanger Research Bureau, New York, and the Department of Anatomy, Harvard Medical School, Boston)

THOUGH there has been much discussion of the nature and function of the vaginal fluid, little is known regarding its quantity. Dickinson¹ described the vagina, when examined by speculum, as 'no more than moist.' Baker and associates,² in laboratory experiments intended to approximate clinical conditions, used 1 c.c. of physiological saline to imitate vaginal fluid. This volume was chosen by a medical subcommittee of the Family Planning Association of Great Britain, though the authors thought it should be rather more.² Textbooks. on gynecology, except in discussions of leukorrhea, are silent regarding the quantity of fluid normally present in the vaginal canal.

To secure more accurate information on this matter measurements of the vaginal fluid of 113 women were made at the Margaret Sanger Research Bureau, in New York.

## Procedure

During the course of routine examinations a dry fenestrated speculum was inserted into the vagina. The entire vaginal wall was swabbed with a sterile absorbent cotton wad which had previously been weighed in a closed container. The wad was immediately replaced in its container and reweighed. The increase in weight showed the amount of vaginal fluid recovered. Records were made of the age of each patient, the usual length of her cycle, the number of days since the onset of her last menstrual period and whether she had had intercourse or used a douche during the preceding 24 hours. Each patient was also examined for possible vaginal or cervical infection.

### Results

The average weight of the vaginal fluid thus determined for the 113 women examined was found to be 0.76 Gm., with a standard deviation for the group of 0.04 Gm. Among the women who had douched during the previous 24 hours, the average amount was 0.50 Gm. For those showing evidence of infection the average was 1.0 Gm. Intercourse within 24 hours, when not accompanied by douching, did not appear to affect the amount of vaginal fluid.

As the cervical mucus has been found to increase in amount and fluidity at the time of ovulation, it was thought that the quantity of the vaginal fluid might also vary with the time in the cycle. The averages were, therefore, calculated for each 4 day period of the cycle and a graph constructed to show volumes of fluid in such periods, expressed both in days after a preceding

period as well as in days before the next one (Fig. 1). The results show that there is an increase in the amount of fluid in the vagina at the time of expected ovulation, reaching 1 Gm. during the period of 13-16 days before the expected menstruation. Statistical analysis showed a strong probability that this increase is significant.

## Comment

Aside from its general physiological significance, the quantity of vaginal fluid is of interest in connection with the use of certain contraceptives, especially of contraceptive foam tablets. Most of these tablets contain sodium bicarbonate and tartaric acid, compounds which, in the presence of moisture, interact to produce carbon dioxide. This breaks up the tablet and rapidly produces a solution. The resulting sodium tartrate has been found to immobilize sperm rapidly.<sup>3</sup> In addition, most commercial contraceptive tablets contain other ingredients chosen for their spermicidal powers.

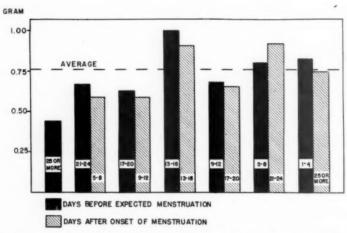


Fig. 1.—The volume of vaginal fluid expressed in 4 day periods and related to both previous and succeeding menstruation.

Clinicians have been divided in their opinion regarding the time at which the tablets dissolve. Some presume that the tablets dissolve in the vaginal fluid, providing a solution which mixes with the semen. Others believe that the semen is the chief solvent, and that the semen is effectively stirred by the bubbles of carbon dioxide which the reaction produces.

As most commercial contraceptive foam tablets weigh about 1 Gm. or more, the average value of 0.76 Gm. of vaginal fluid found, or even the 1 Gm. during the mid-monthly peak, appears inadequate for solution of the tablets. In clinical use, moreover, the tablets will be exposed to a much smaller portion of the fluid than was recovered from the entire vagina. Some clinicians suggest that the lubricating fluid which may accompany sexual response is a factor in solution of the tablets. Since this fluid is produced by the Bartholin glands at the external orifice it will not reach the tablet before intercourse begins and will probably be transported inward in only small amounts. Any increase in cervical secretion during sexual arousal would normally occur just prior to the arrival of the semen, and could therefore hardly be an important factor in the solution of the tablet.

Although the osmotic effect of the tablet may possibly withdraw some additional fluid from the vaginal wall, it seems probable that the effectiveness of the tablet depends chiefly upon its reaction with the semen.

# Summary

1. The average quantity of fluid recovered from the vaginas of 113 women by swabbing the entire vaginal wall, while examining with a dry fenestrated speculum, was 0.76 Gm.

2. During the period of 13 to 16 days before the expected menstruation the amount was 1 Gm.

3. Since contraceptive foam tablets are exposed to only a portion of this fluid it is probable that reaction with the semen is more important in their protective activity than is solution in the vaginal fluid.

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# A STUDY OF VAGINAL ACIDS\*

CHARLES A. HUNTER, JR., M.D.,\*\* AND HAROLD J. NICHOLAS, Ph.D., KANSAS CITY, KAN.

(From the Department of Obstetrics and Gynecology, University of Kansas School of Medicine)

In THE study of factors which influence vaginal acidity, it became of interest to study the chemical nature of vaginal fluid in some detail. It seemed reasonable, for example, that any acids present might exert some influence on the pH of the fluid. The present investigation was undertaken with this objective in mind. Recently Haour, Conti, and Guyot<sup>2</sup> and Berton<sup>3</sup> have called attention to the presence of amino acids in vaginal fluid.

## Materials

The 31 patients (21 normal and 10 abnormal) included in this study were regularly menstruating women, ranging from 13 to 40 years of age, who had no obvious metabolic disturbances. Women with pelvic disease, other than vaginitis, were excluded from this study. All of the patients refrained from douching or coitus for a minimum period of 72 hours prior to collecting the samples.

After the patient was placed in lithotomy position, the vagina was exposed with a sterile, unlubricated bivalve speculum which was inserted to about one half the depth of the vagina. Specimens for the smear were taken with sterile cotton-tipped applicators ahead of the speculum from the upper vagina. The smears were classified according to Schröder's method. Wet mounts were made for examination of trichomonads. Vaginal and cervical pH readings were taken with a Beckman model G pH meter using glass electrodes.

Following the foregoing procedures, the vagina was washed with 100 ml. of triple-distilled sterile water by means of a special glass syringe. The vaginal washings were collected and placed into sterile glass containers. These vaginal washings were frozen and taken to the laboratory.

# Methods and Results

Reagents.—All solvents were analytical reagent grade and were distilled before use. Control amino acids were obtained as "chromatographically pure" dextrolevorotatory samples. Distillations, including those by steam, were performed in all glass apparatus. The general procedures described by Block, Durrum, and Zweig<sup>5</sup> for chromatography of aliphatic and amino acids were followed, and all chromatography was performed at room temperature in an airconditioned room. Whatman No. 1 paper was used throughout the investigation.

<sup>•</sup>This investigation was supported (in part) by research grant E-613 (C) from the National Institutes of Health, United States Public Health Service.

••Present address, Department of Obstetrics and Gynecology, Indiana University Medical Center, Indianapolis, Ind.

Detection and Determination of Volatile Fatty Acids.—An aliquot of the washings, usually about 50 ml., was made alkaline to pH 11 with sodium hydroxide. Excess water was distilled from the mixture until 5-10 ml. of original washing remained. This volume was acidified with sulfuric acid (to pH 2-3) and steam distilled until 10-15 volumes of distillate were collected. The distillate was again adjusted to pH 11 and dry distilled to 10-15 ml. volume. This residue (the distillate from the latter distillation was discarded) was adjusted to fixed volume with distilled water and aliquots were used for chromatographic scanning and quantitative evaluation for pyruvic acid. Aliquots were converted to the hydroxamates as described by Block and associates and pyruvic acid was detected in the solvent system, water-saturated phenol, using a spot of authentic pyruvic acid as a control ( $R_{\rm f}=0.56$ ). Some quantitative determinations of pyruvic acid were then made on a number of vaginal washings by the method of Friedemann and Haugen.

Detection of Nonvolatile Acids.—Frozen washings were thawed and centrifuged. The supernatants were dry distilled until approximately 10 ml. was obtained. The residue was steam distilled (to eliminate all free volatile materials) until 30-50 ml. of distillate was collected (distillate discarded). The residue from this distillation was boiled to low volume and adjusted to 2.0 ml. with distilled water. Aliquots of this dilution (0.05 to 0.10 ml.) were spotted on paper, with a current of warm air to facilitate removal of solvent. Spots were usually 0.5-1 cm. in diameter. Of a number of solvent systems investigated the mixture n-butanol: acetic acid: water =  $250:60:250^{7}$  and the mixture absolute ethanol: concentrated ammonia: water =  $80:5:15^{8}$  were found to separate aliquots into a number of discrete spots satisfactorily. Four of these proved to be amino acids on spraying the paper with ninhydrin (0.25 Gm. in 100 ml. of acetone). The  $R_{\rm f}$  values of these spots in the solvent system, absolute ethanol: concentrated ammonia: water = 80:5:15, were as follows:

SPOT NO.		$\mathbf{R}_{\mathbf{f}}$
1		0.15-0.17
2		0.20-0.22
3	9	0.42-0.46
4		0.58-0.62

Spot 1 was of lesser intensity in all washings and was not further investigated during the present study. Although several possibilities were present for other amino acids, the Rf values of spots 2, 3, and 4, respectively, corresponded well with those for glutamic acid (0.22), threonine (0.45), and leucine (0.67), when the latter acids were chromatographed in the same solvent system. In order to insure the identity of these spots, twenty-four 0.05 ml. portions of an individual vaginal concentrate were spotted on a 46 by 57 cm. Whatman No. 1 sheet at intervals of 4 cm. along the starting line. After development (about 8 hours) a control strip representing separation of one of the spots was cut from the edge of the paper and sprayed to delineate the position of the spots on the rest of the sheet. Control strips were then cut lengthwise along the paper to include all areas representing spots 2, 3, and 4, respectively. Each strip was cut into small pieces and extracted three times with 20 ml, portions of hot absolute ethanol. The combined elutions were distilled to dryness in vacuo and redissolved in 0.2 ml. absolute ethanol. Aliquots of this solution were then spotted on paper individually and superimposed on a 5 µg spot of the suspected amino acid; a spot of control amino acid alone was chromatographed along with these two spots. There was no separation of spots (unknown, mixtures, or controls) for each of the unknowns in

the system n-butanol: acetic acid: water = 250:60:250 (R<sub>f</sub> glutamic acid = 0.37; threonine = 0.36; leucine = 0.72 in this system<sup>5</sup>) or in a two-dimensional system using water-saturated phenol, ammonia (first direction) and watersaturated collidine (second direction).

The position of lactic acid in these washings was not exactly ascertained; it has been reported to be present in vaginal mucosa in rather large quantities. Although some of it was probably lost in the steam distillations performed (traces were consistently found in the distillates by the method of Umbreit, Burris, and Stouffer<sup>9</sup>), most of it should remain in the nonvolatile fraction. When spots of the latter were chromatographed in the system, absolute ethanol: concentrated ammonia: water = 80:5:15 and dipped in bromeresol green solution (0.5 Gm. in 100 ml. 95 per cent ethanol), along with some other spots, a large yellow spot (R<sub>f</sub> 0.53-0.60) consistently showed up in all washings. This was believed to be lactic acid in preliminary studies, but it was not followed in great detail. Further investigation of this and several other spots identified as amino acids is in progress. There was no evident correlation between the degree of vaginal acidity (determined by pH) and the number and relative intensity of spots indicating amino acids.

# Summary

Four acids have been identified in the vaginal washings of all patients examined during this investigation: pyruvic acid, and the amino acids, glutamic acid, threonine, and leucine. Pyruvic acid appeared to be present in trace amounts. Quantitative assessment of the others has not been determined. Several other amino acids were indicated in a number of the washings. but their presence was not consistent for all samples investigated. Lactic acid was probably present in all samples, but its presence was not definitely verified.

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# VAGINAL FLUID SUBSEQUENT TO PANHYSTERECTOMY\*

JOHN I. PERL, M.D., GEORGE MILLES, M.D., AND YUKIO SHIMOZATO, M.D., CHICAGO, ILL.

(From the Departments of Surgery and Pathology, Augustana Hospital)

THE purpose of this paper is to present data regarding the volume and origin of the vaginal fluid subsequent to panhysterectomy with or without oophorectomy.

It is generally assumed that since the lining of the normal vagina is devoid of glands, its entire moisture content is derived from the secretions of the endometrial, endocervical, and cervical glands, in spite of the fact that after complete removal of the uterus, tubes, and ovaries, moisture continues to be found in the vagina. Although in some instances vaginal fluid may be produced by ectopic endometrial or cervical glands in the vaginal wall, one must either assume that every vaginal wall is seeded with aberrant glands or that there are other sources of the vaginal fluid in the absence of the entire uterus.

Such was the problem in a 60-year-old multipara who was subjected to surgical treatment for a large hydrocolpos 18 months after panhysterectomy.¹ No ectopic glands were found on histological examination of multiple sections from the sequestrated segment of the vagina which formed the wall of the hydrocolpos. Was the fluid the product of ectopic glands which remained undetected, was it a transudate via the vaginal wall, or was it derived from the desquamating epithelium of the sealed-off vaginal tube?

#### Material

To obtain information upon which a valid answer to these questions could be based, the following studies were carried out on 26 patients who had been subjected to panhysterectomy with or without oophorectomy 7 months to 22 years previously.

1. The vagina, exposed through a bivalve speculum, was sponged dry with cotton and a tampon weighed to two decimals was inserted.

2. To prevent contamination with urine, a Foley eatheter was introduced into the bladder for the duration of the test.

3. Twenty-one to 27 hours later the tampon was removed and reweighed. The catheter was removed from the bladder *after* the tampon had been removed from the vagina in order not to contaminate the introitus with urine.

4. The findings were interpreted on the basis of the presence or absence of ovarian tissue and/or the administration of hormones.

Patients who had gross evidence of leukorrhea or other symptoms of colpitis were excluded.

 $<sup>^{*}</sup>$ This work was supported in part by funds from the Nelson M. Percy Research Foundation.

TABLE I

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PATIENT	AGE	PATHOLOGICAL FINDINGS	OPERATION	REMAIN- ING OVARY OR OVARIES	HORMONE THERAPY AT THE TIME OF THE TEST	DURATION OF TEST (HOURS)	AMOUNT OF VAGINAL FLUID FOUND DURING TEST PERIOD (GM.)	AMOUNT OF VAGINAL FLUID CALCU- LATED FOR 24 HOURS (GM.)
A. K.	63	Endometrial carcinoma	Abdominal hyster- ectomy, bilateral oophorectomy (1954)	0	0	24	1.65	1.65
G. C.	53	Fibromyomas	Abdominal panhyster- ectomy, bilateral salpingo-oopho- rectomy (1946)	0	0	22	1.55	1.68
H. C.	38	Chronic pelvic inflammatory disease; fibroids	Abdominal panhyster- ectomy, right salpingo-oopho- rectomy, left salpin- gectomy (1950)	Yes	0	26	2.45	2.14
M. L.	65	Fibroid uterus	Abdominal panhyster- ectomy, bilateral salpingo-oopho- rectomy (1949)	0	0	22	1.55	1.68
J. B.	68	Uterine prolapse	Vaginal hysterectomy, anterior and pos- terior colporrhaphy (1936)	Yes	0	27	1.65	1.44
S. S.	56	Fibromyomas	Abdominal panhyster- ectomy, bilateral salpingo-oopho- rectomy (1947)	0 .	0	25	1.72	1.65
M. K.	50	Fibromyomas	Abdominal total hysterectomy (1954)	Yes	Yes	27	2.19	1.92
J. C.	56	Fibromyomas	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy (1953)	0	0	27	1.72	1.51
E. P.	42	Fibroids	Abdominal total hysterectomy, right salpingo-oopho- rectomy (1956)	Yes	Yes	23	2.00	2.08
I.M.	45	Fibroids	Abdominal total hysterectomy (1955)	Yes	0	25	2.08	1.96
A. S.	53	Fibroids	-Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy (1954)	0	Yes	26	2.15	1.97
E. C.	49	Fibroids	Abdominal total hysterectomy (1952)	Yes	Yes	25	2.02	1.92
J. H.	42	Fibroids	Abdominal total hysterectomy, right salpingo-oopho- rectomy (1951)	Yes	Yes	25	2.03	1.92
P. N.	45	Fibroids	Abdominal total hysterectomy, right salpingo-oopho- rectomy (1956)	Yes	0	22	1.95	2.08

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TABLE I (CONT'D)

1							AMOUNT	
PATIENT	AGE	PATHOLOGICAL FINDINGS	OPERATION	REMAIN- ING OVARY OR OVARIES	HORMONE THERAPY AT THE TIME OF THE TEST	DURATION OF TEST (HOURS)	OF VAGINAL FLUID FOUND DURING TEST PERIOD (GM.)	AMOUNT OF VAGINAL FLUID CALCU- LATED FOR 24 HOURS (GM.)
C. W.	49	Fibroids	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy (1950)	0	0	24	1.20	1.20
M. S.	47	Fibroids	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy (1950)	0	0	21	1.25	1.44
A. N.	46	Fibroids	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy (1952)	0	0	24	1.65	1.65
м. т.	50	Fibroids	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy	0	Yes	26	2.00	1.84
H. S.	61	Endometrial carcinoma	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy (1948)	0	0	26	1.68	1.56
V. S.	62	Fibroids	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy (1942)	0	0	27	1.62	1.44
М. М.	62	Prolapse; fibroids	Vaginal hysterectomy, anterior and pos- terior colporrhaphy (1949)	Yes	Yes	23	1.85	1.92
E. R.	56	Fibroids	Abdominal total hysterectomy (1949)	Yes	0	25	1.70	1.63
B. W.	40	Chronic gran- uloma of myometrium; foreign body	Abdominal total hysterectomy (1957)	Yes	0	24	2.07	. 2.07
A. J.	43	Fibroids; polyps	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy	0	Yes	26	2.18	1.99
V. C.	54	Fibroids	Abdominal total hysterectomy, bi- lateral salpingo- oophorectomy	0	Yes	23	2.05	2.12
A. N.	50	Fibroids	Abdominal total hysterectomy, bilateral salpingo- oophorectomy	0	Yes	24	1.95	1.95
Total			•			639	47.91	1.80 (averag

# **Findings**

A measurable quantity of vaginal fluid was formed by every subject during the test period of 21 to 27 hours. The 26 women, varying from 38 to 68 years of age, produced a total of 47.91 Gm. of vaginal fluid which, calculated for a uniform period of 24 hours, averaged 1.78 Gm. per subject. In the absence of ovaries and hormone therapy 10 women (46 to 63 years, average 55.8 years) produced a total of 15.59 Gm. in 242 hours, or an average of 1.54 Gm. each calculated for 24 hours. Six women (38 to 68 years, average 48.6 years), whose ovaries were present, produced 11.90 Gm. in 149 hours, or an average of 1.89 Gm. each calculated for 24 hours. Five women (43 to 53 years of age, average 50 years), receiving hormone therapy alone, produced a total of 10.33 Gm. in 125 hours, an average of 1.97 Gm. each calculated for 24 hours. Five women (42 to 62 years, average 49 years), with ovaries and receiving hormone therapy, produced 10.09 Gm. in 123 hours, an average of 1.95 Gm. each calculated for 24 hours.

Thus the presence of ovaries and/or hormone therapy resulted in the formation of the largest amounts of vaginal fluid although this variation was somewhat less pronounced in the older age group.

## Comment

In the anatomically intact and physiologically normally functioning genital unit, the vaginal fluid consists of (a) morphological elements of the common vaginal flora and cast-off epithelium; and (b) secretion of the endometrial, endocervical, and cervical glands.

Doederlein<sup>2</sup> was first to point out that the whitish curdlike material in the vagina during pregnancy is derived from castoff epithelium of the vagina. Papanicolaou. Traut, and Marchetti<sup>3</sup> emphasized that the two important functions of the vaginal epithelium, the secretion of glycogen and the cornification and exfoliation of the superficial epithelial layers, represent a holocrine type of secretion.

After panhysterectomy, but with retained ovarian function, the desquamating epithelial elements and bacterial flora remain, but the glandular secretions are *absent* from the vagina. Very much the same situation will hold if the ovaries are also removed and hormone therapy instituted.

On the other hand, in the total absence of hormonal stimulation the number of layers of vaginal epithelium is reduced to 3 or 4, its glycogen production is abolished, and cornification ceases except under pathological conditions such as prolapse. This is the atrophic, pale, smooth, shiny, vulnerable vaginal mucosa of the postmenopausal individual. In the absence of glycogen in the desquamating cells, the lactic acid-producing bacteria of the vagina are deprived of this important nutritive substance and the pH of the vaginal contents is altered. Nevertheless some fluid continues to be formed, presumably a transepithelially migrating fluid comparable to the transepidermal "insensible" water loss through the skin, i.e., a true transudate via the vaginal wall.

Evaporation of this fluid is prevented because of the fact that the vaginal surfaces lie in contact, and this fluid keeps the vagina moist while it slowly seeps toward the more exposed introital segment from where it finally disappears, leaving a meager residue of cellular debris made up of the slowly desquamating atrophic vaginal epithelium and bacteria.

How does the view that the vaginal moisture after panhysterectomy is a transepithelially migrating fluid jibe with the concept of the so-called transepidermal insensible water loss?

We recovered an average of 1.54 Gm. of fluid per day from the vagina of patients without ovaries and/or hormone medication. The over-all average of vaginal fluid formed per day was 1.78 Gm.

One hundred fifty-five total colpectomies were performed on the Surgical Services in Augustana Hospital from 1908 to 1958. The excised vaginal integument was measured in 21 cases from 1954 to 1958. It ranged from 62 sq. cm. to 162 sq. cm. with an exceptional instance in which it was 300 sq. cm. The average was slightly over 100 sq. cm. The vaginal integument, measured at autopsy, was 49 sq. cm., 71 sq. cm., 70 sq. cm., 82 sq. cm., and 90 sq. cm., in 5 septuagenarians and 99 sq. cm. and 158 sq. cm. in 2 patients in the sixth decade. Thus a round figure average of 100 sq. cm. of vaginal surface area is a reasonable basis for calculation in the postmenopausal state.

The skin surface of an adult woman approximates 16,000 sq. cm.<sup>5</sup> The insensible water loss via skin is about 350 Gm. per day,6 or 0.021 Gm. per square centimeter per day. Thus the vagina, the surface of which is about 1/160 of the total body surface, produces an average of 1.78 c.c. per 24 hours, which approximates  $\frac{1}{160}$  of the transepidermal water loss from the total skin surface, namely, 2.10 Gm. per day.

# Summary

1. Subsequent to panhysterectomy 26 individuals yielded a total of 47.91 Gm. of fluid during 639 hours, an average of 1.8 Gm. per subject per 24 hours. (Range 1.2 to 2.14 Gm. per 24 hours.) (Table I.)

2. Ten patients, following panhysterectomy and oophorectomy and without hormone therapy, yielded an average of 1.54 Gm. per day of vaginal fluid. (Range 1.2 to 1.68 Gm. per 24 hours.)

3. Sixteen patients with intact ovaries with or without hormone therapy yielded an average of 1.93 Gm. per day of vaginal fluid. (Range 1.44 to 2.14 Gm. per 24 hours.)

4. It is suggested that the vaginal moisture, following panhysterectomy, is largely derived from a transepithelially migrating fluid comparable in dynamics to the transepidermal insensible water loss through the skin.

5. The daily average amount of recoverable fluid from the vagina following panhysterectomy (1.8 Gm.) approximates a computed figure obtained from the calculated transepithelial water loss from an area approximating the vaginal surface (2.1 Gm.).

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# PRIMARY MALIGNANT MELANOMA OF THE VAGINA

Donald R. Freund, M.D.,\* Eugene E. Kegel, M.D., and John H. Dugger, M.D., Philadelphia, Pa.

(From the Department of Obstetrics and Gynecology, Episcopal Hospital)

PRIMARY malignant melanoma of the vagina is an uncommon lesion. Even so, the first authentic case appears to have been reported as long ago as 1887 by Parona¹ in Italy. In 1948 Mino, Mino, and Livingstone² reviewed the literature and were able to collect only 18 cases including one of their own. Another of these 18 cases was reported in 1944 by Taylor and Tuttle,³ who were unable to decide, because of its location when first seen, whether the lesion actually originated in the vagina proper or in the cervix uteri. Since 1948 there have been 10 cases reported in the literature.⁴-13

Most malignant melanomas of the vagina seem to occur in individuals over 60 years of age although the lesion has been recorded in a woman of only 28 years.<sup>2</sup> The usual presenting symptom is vaginal bleeding of short duration. Vaginal discharge with or without blood streaking is also common. Other symptoms may include rectal tenesmus, dyspareunia, and abdominal discomfort or fullness.

The lesion when first seen by the physician may be found in any portion of the vagina, but it usually appears just within the introitus. Most are 1.5 cm. or larger when first detected, although there may be multiple small lesions. The tumor is usually blue-black or black in color. Ulceration is common and the lesion may or may not be tender on manipulation.

Histologically, malignant melanomas of the vagina appear similar to malignant melanomas elsewhere in the body. The cellular forms are variable in size and staining quality, and often show atypical mitoses. Brown or dark brown pigment is found scattered throughout, both intra- and extracellularly. They are usually granular and vary in quantity from one portion of the tumor to another. The pigment fails to react with iron stains.

There is much discussion in the literature as to the origin of melanotic cellular elements in the vagina. Some authors doubt the existence of melanin production by cells in the vagina and state that all malignant melanomas of the vagina are secondary to some lesion elsewhere. Ewing, however, lists 4 possible origins: (1) from specific mesoblastic cells, chromatophores, which originate very early in the embryo; (2) from nerve cells of sensory end organs (Meissner's corpuscles) which produce the clear cells of the quiescent adult nevus and often assume the function of pigment production

<sup>\*</sup>Present address: 74 Washington Avenue, Northampton, Mass.

(most skin melanomas are thought to arise from this derivation); (3) from epithelium which has taken on the role of pigment production; and (4) from endothelial cells of blood or lymph vessels or of nerve trunks. Robert Meyer has shown that the human vagina develops from the urogenital sinus which normally contains pigment,<sup>5</sup> while Hajikano<sup>7</sup> quotes Nuerenberger as saying that the vaginal epithelium may normally have pigment-forming potentialities.

The method of treatment is controversial and may include simple or radical surgery alone or in combination with irradiation, or irradiation alone. The recommended procedure at present appears to be surgery with wide excision of the local lesion. Some authors include radical lymph node dissection. Most patients succumb to the disease within a year after its discovery regardless of the type of therapy. One patient reported on by Mino, Mino, and Livingstone survived 15 years in spite of local recurrence 4 years after first being seen. Complete pelvic evisceration attempted by Mino, Livingstone, and Hynes<sup>6</sup> resulted in death of the patient the day following nephrostomy performed 5 days after the evisceration. These authors state categorically that irradiation is not recommended and that surgery is not to be recommended routinely, but they offer no further therapeutic suggestions.

Because malignant melanoma of the vagina is such an uncommon lesion and because our 2 patients were treated with radioactive cobalt, a type of treatment which has not previously been described in the literature for such lesions, we are reporting these cases.

# Case Reports

Case 1.—Mrs. C. A., a 73-year-old white widow, para i, gravida i, who experienced an uneventful menopause at 45 years of age, was admitted to the Episcopal Hospital on Jan. 1, 1956, complaining of intermittent vaginal bleeding of 2 months' duration. Associated symptoms were a 5 pound weight loss, stress incontinence, frequency of urination, intermittent lower abdominal pain, weakness, and vulvar pruritus, all of approximately the same duration as the bleeding.

On admission the patient's blood pressure was 170/100. She was obese and the following physical abnormalities were noted: a 1 by 2 cm. wrinkled, elevated mass in the intergluteal fold (right side), slight cardiac enlargement to the left, liver enlargement 3 fingerbreadths below the right subcostal margin, and bilateral lower abdominal tenderness. Varicosities and 1 plus edema were present in both lower extremities.

A chest x-ray revealed the presence of a small nodule within the medial segment of the right middle lobe, and left ventricular enlargement. The nature of the right pulmonary nodule was not further amplified, but it was felt that it might represent a metastatic lesion from the vaginal tumor. An intravenous pyelogram and complete bone survey were entirely normal. An electrocardiogram was interpreted as showing left ventricular enlargement and possible myocardial damage.

Cystoscopic examination demonstrated an elevation of the bladder trigone probably due to the vaginal tumor. The bladder mucosa was normal but the degree of bladder fixation suggested serosal and bladder wall involvement.

Funduscopic examination disclosed no evidence of melanoma, but chronic hypertensive changes of moderate degree were noted.

Pelvic examination revealed a moderately severe nonspecific vulvitis. There was a grayish-white necrotic, extremely friable, fungating mass on the anterior vaginal wall extending from the cervix to within a centimeter of the urethral meatus. The cervix was continuous with the vaginal mass. The uterus could be felt with difficulty as a small,

symmetrical organ in the anterior position. The adnexa seemed normal but there was slight parametrial induration and fixation on the right side. These findings were confirmed by rectal examination.

A biopsy of the vaginal mass was performed without difficulty. However, the external cervical os could not be identified and attempts to perform a dilatation and

Fig. 1.

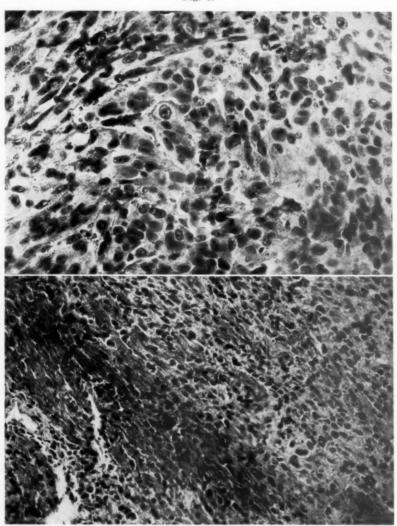


Fig. 1.—Case 1. Primary malignant melanoma of vagina.  $(\times 450; \text{ reduced } \frac{1}{36}.)$ Fig. 2.—Case 2. Primary malignant melanoma of vagina.  $(\times 255; \text{ reduced } \frac{1}{36}.)$ 

curettage were unsuccessful. The tumor tissue, reported by the pathology department to be from a malignant melanoma, was grossly brownish in color. Histologic examination of the sections demonstrated highly cellular tumor composed of sheets of oval to polygonal cells with prominent rounded nuclei. Mitoses were frequent; in some fields there was a high degree of nuclear pleomorphism. In some areas the tumor cells were elongated and more widely spaced. Variable numbers of tumor cells contained brown pigment granules characteristic of malignant melanoma. The pigment did not react with Prussian blue stain for iron (Fig. 1).

An excision biopsy of the intergluteal mass was reported as indicating a soft fibroma of the skin.

We felt that the patient's poor cardiovascular status, obesity, and the degree of bladder involvement with evidence of possible lung metastasis were contraindications to surgery. Therefore, we sought the consultation of Dr. Stanley P. Reiman at the Lankenau Hospital in Philadelphia, and arrangements were made for the patient to be treated there with a course of cobaltée beam therapy delivered to the pelvis. The tumor dose was calculated at 6,000 r. Local regression of the tumor resulted but metastases to the lumbar spine, left ilium, and both lung fields were later demonstrated.

Further palliative cobalt therapy to the sites of bone metastases relieved the patient of the bone pain although her life was probably not prolonged to any great extent. On July 26, 1956, she died with generalized metastases.

CASE 2.—Mrs. F. S., a 78-year-old woman, para ii, gravida ii, who had an uneventful menopause at the age of 47 years, was admitted on April 18, 1955, complaining of intermittent vaginal bleeding of one month's duration. A pelvic examination and Papanicolaou smear 6 months prior to this admission had disclosed no abnormal findings. One year prior to this admission, however, the patient had had a basal cell carcinoma removed from the bridge of her nose by a dermatologist.

When she was first seen with the present complaint, the positive physical findings included the presence of many pigmented moles on the trunk, none of which had undergone any recent change. There were deformities typical of rheumatoid arthritis in the extremities.

Pelvic examination disclosed senile atrophic changes of the vulva. The vagina contained a semisolid dark granular tumor which arose from the posterior vaginal wall and filled up the vault. The uterus was normal to palpation. In the course of removal of a portion of the tumor for biopsy the posterior fornix was perforated and required suture repair.

The specimen was reported by the pathologist to represent a malignant melanoma. It was grossly gray in some areas and brown in others. Histologically, sheets of tumor cells were closely packed and exhibited infrequent mitoses. The cells were polygonal and ovoid in shape with prominent oval nuclei. There was a slight to moderate degree of nuclear pleomorphism. Moderately coarse granules of brownish pigment which did not react when stained for iron were found both within and about the tumor cells (Fig. 2).

A chest x-ray revealed both ventricles to be enlarged and the aorta to be markedly tortuous and sclerotic. There was also a suggestion of auricular enlargement but there was no evidence of metastatic disease. An electrocardiogram was compatible with myocardial damage.

The patient's poor medical status and age contraindicated definitive surgical treatment. A course of cobalt<sup>60</sup> therapy was given at the Lankenau Hospital after which the vaginal bleeding stopped and the vaginal tumor regressed.

The patient died approximately 5 months after treatment at which time she had extensive generalized metastases.

## Summary

- 1. Ten cases of primary malignant melanoma of the vagina have been collected from the literature to be added to those assembled in 1948 by Mino, Mino, and Livingstone.
- 2. Two new cases are also described bringing the total number of reported cases to 30.

- 3. Both of the new patients sought medical aid, chiefly because of vaginal bleeding, which is the most common complaint noted in the cases reported in the literature.
- 4. Both of the new patients received cobalt<sup>60</sup> therapy. Although temporary symptomatic relief resulted, each patient developed metastases and both died within 7 months.

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# HEMANGIOPERICYTOMA OF THE VULVA\*

Luiz Meleiro de Sousa, M.D., and Abraham F. Lash, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology and the Department of Pathology, Michael Reese Hospital)

UP TO Dec. 31, 1954, Stout¹ collected 207 cases of hemangiopericytoma including 3 cases in the vulva and vagina. To our knowledge, however, these 3 cases have not been reported and the first reported case of hemangiopericytoma of the vulva is herein presented.

# Case Report

Patient S. K., admission No. G12335, a white 44-year-old gravida iv, para iii, entered Michael Reese Hospital on April 17, 1957, because of menometrorrhagia, postcoital spotting of one year's duration, and painless vulvar swelling of 2 or 3 months' duration. Her past history was not remarkable. She was an only child. Her mother, age unknown, had died of a brain tumor; her father had died of a liver condition. His age and the character of the condition were unknown. Physical examination revealed the essential findings limited to the pelvis as follows: a doughy to cystic mass the size of a hen's egg in the left labium majus; a relaxed pelvic floor with rectocele; a fibroid uterus the size of a 10 weeks' pregnancy, with a cervical polyp and chronic cervicitis. Chest x-ray revealed no pulmonary abnormality.

On April 18, 1957, an operation was performed which included vaginal hysterectomy, repair of the rectocele, perineorrhaphy, excision of the left labial mass, and excision of the left Bartholin gland.

The postoperative course was uneventful and repeated subsequent examinations revealed no pelvic lesions. The pathological report (57PI996 A, B, C) included:

A. Leiomyomas of the uterus; one markedly cellular. The impression was that this was a benign tumor although there were a number of mitotic figures. Two cervical polyps each measuring 1.2 by 1.8 cm.

B. Bartholin gland with large dilated duct, plus skeletal muscle and vascular tissue.

C. The mass removed from the left labium majus was described grossly as an irregular purplish-gray encapsulated soft tissue tumor. Cut sections revealed gray-purple smooth homogeneous tissue.

Microscopically, this tumor was formed by a proliferation of small vessels of the capillary type. In some zones they were easily recognized with hematoxylin and eosin stain (Fig. 1), while in others they were apparent only after the Gomori method of silver impregnation for reticular fibers was used (Fig. 2). The capillaries were separated by various amounts of loose connective tissue. Outside the reticular sheath of the capillaries, diffusely scattered in some places and more closely packed in others, were numerous

<sup>\*</sup>Presented before the Chicago Gynecological Society, Nov. 15, 1957.

cells, some rounded, some spindle-shaped, but most of them ovoid with large nuclei containing fine reticular chromatin and prominent nucleoli (Fig. 4). The cytoplasm of the cells was not prominent, the nucleus making up almost the entire cell. Some nuclei were hyperchromatic but no mitotic figures were seen. A network of reticular fibers was present between the cells (Fig. 3).

This type of tumor has been called a hemangiopericytoma.

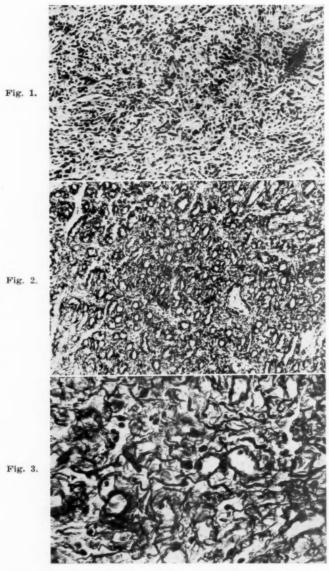


Fig. 1.—Section of the tumor showing marked cellularity and pleomorphism. Note numerous endothelium-lined spaces. (Hematoxylin and eosin.  $\times 200$ ; reduced  $\frac{1}{16}$ .)

Fig. 2.—An area from the same section as Fig. 1 stained for reticulum to demonstrate the numerous minute vascular channels. (Gomori's reticulum stain.  $\times 200$ ; reduced  $\frac{1}{16}$ .)

Fig. 3.—Higher power view of Fig. 2 showing the rich network of reticular fibers and the vascular channels. (Gomori's reticulum stain.  $\times 400$ ; reduced  $\frac{1}{16}$ .)

Hemangiopericytomas of the uterus have been misdiagnosed as cellular myomas, so reticular stains were done in one of the myomas that was markedly cellular but no evidence of vascular tumor was found.

#### Comment

As far as the distribution of hemangiopericytoma is concerned, it is worth emphasizing that the uterus occupies the third place (16 cases), surpassed only by the leg, thigh, and gluteal region group (46 cases) and the retroperitoneal, mesenteric, and omentum group (21 cases) in the 207 cases collected by Stout¹ up to Dec. 31, 1954. The complete list of cases is as follows: thyroid 1; orbit 5; eye 1; meninges 3; brain 1; stomach 8; intestines 4; retroperitoneum, mesentery, and omentum 21; oral cavity and pharynx 6; liver 3; salivary glands 2; mediastinum 5; larynx and trachea 3; pleura 1; lung 1; nasal cavity and sinuses 2; uterus 16; female breast 2; male breast 1; ovary 1; vulva and vagina 3; prostate 2; hands 12; arm and forearm 10; leg, thigh, and gluteal region 46; feet 4; back 9; chest and abdominal wall 10; neck 7; face 7; scalp and ears 5; and bones 5.

Recently a few more hemangiopericytomas of the uterus have been reported.<sup>2-6</sup>

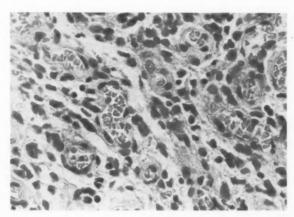


Fig. 4.—This section demonstrates the numerous pericytes making up most of the tumor. Note the prominent capillaries lined by hypertrophic endothelial cells with no significant degree of endothelial cell proliferation. (Hematoxylin and eosin.  $\times 400$ ; reduced  $\frac{1}{16}$ .)

Prior to 1954 when Pedowitz and associates<sup>2</sup> published their paper, all of the 9 uterine hemangiopericytomas diagnosed were benign. These authors, reviewing a group of uterine tumors diagnosed as hemangio-endotheliomas and sarcomas, found that 4 were hemangiopericytomas. Recurrence of the tumor was noted in 2 cases, one with invasion and one with metastasis.<sup>2</sup> A short follow-up did not reveal malignant behavior in the 5 cases described by Greene and Gerbie in 1954.<sup>3</sup> Pedowitz,<sup>4</sup> in 1955, added one more case that can be considered malignant. The case reported by Tupper<sup>5</sup> is too recent to be classified.

Although Fisher<sup>7</sup> thought he could risk a prognosis on the case he reported, almost all authors agree that the diagnosis of benign or malignant tumor cannot be made on histological grounds, the real nature of the lesion being disclosed only by the subsequent clinical course. Therefore, unless metastases are present the benign or malignant nature of hemangiopericytoma cannot be determined histologically. Hyperchromatosis, increased mitosis, and the presence of

tumor cells within lymphatics do not necessarily presage a malignant course. In the fatal case of Pedowitz' series these criteria of malignancy were absent. One patient is alive and well 11 years after hysterectomy, despite the finding of the tumor cells within the lymphatics of the tumor.<sup>2</sup>

Grossly, the hemangiopericytomas have no diagnostic characteristics. Although some are red or purplish and may resemble capillary hemangiomas, such colors are not present in most of them. This should be expected if we recall that some capillaries do not contain erythrocytes and most of them are collapsed and separated by various amounts of connective tissue and pericytes. Some authors have been impressed by the yellow color present in some tumors, which may eventually suggest a diagnosis. Size and consistency are variable. Calcification may be found. Although grossly some appear to be encapsulated, they usually lack a true capsule.

Microscopically, the tumor is formed by a proliferation of capillaries lined by normal endothelial cells which are separated from the surrounding tumor cells by reticular sheaths. Most of the capillaries are inconspicuous with the usual stains and can be demonstrated only when reticular stains are used. This reticular sheath can attain an appreciable thickness and some of the tumors presenting this feature ultimately were proved to be malignant.8 The cells packed around the capillaries may show marked morphological variation—rounded, ovoid, or spindle-shaped, with round or ovoid vesicular nuclei, usually leptochromatic, containing a single small nucleolus and a well-marked nuclear membrane.<sup>5</sup> In some cases a clear zone around the nucleus can be seen. This variation in the form of the cells should be expected if the relationship between the pericyte and smooth muscle cells is accepted. The cytoplasm is described as scanty by some authors and as abundant by others.<sup>5</sup> Reticular fibers can be seen between the cells.

We wish to thank Dr. A. Rubenstone, Associate Pathologist, Michael Reese Hospital, for all his assistance. Dr. R. R. Greene was kind enough to examine the slides and he agreed with the diagnosis. Dr. Arthur Purdy Stout also studied the slides and agreed with the diagnosis of hemangiopericytoma but thinks that the tumor also presents features of hemangioendothelioma and lipoma and can therefore be classified as a mesenchymoma.

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# ADENOCARCINOMA OF THE RECTOVAGINAL SEPTUM PROBABLY ARISING FROM ENDOMETRIOSIS\*

S. R. LASH, M.D., AND A. I. RUBENSTONE, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology and the Department of Pathology, Michael Reese Hospital)

ALTHOUGH carcinoma arising from endometriosis in the ovary and endometrial sarcoma arising from areas of endometriosis are not rare,<sup>2-15</sup> the only report of primary adenocarcinoma of the rectovaginal septum arising from endometriosis which we could find after a careful review of the current literature was that of Dockerty and associates.<sup>1</sup> They found 5 cases previously reported in the European literature<sup>16-20</sup> and more recently reviewed.<sup>21, 22</sup> Dockerty and his associates then described 2 new cases of this disease.

The criteria for acceptance of adenocarcinoma as arising from endometriosis were outlined by Sampson<sup>12</sup> in 1925 as follows: (1) the presence of a pre-existing nodule of endometriosis at the site of the malignant neoplasm; (2) the certainty that the carcinoma has its origin in the area of endometriosis and does not merely represent invasion or metastasis from another site; (3) the demonstration of transition between the benign and malignant components. The cases reported by Dockerty met the first two criteria and he felt that the insistence upon the third criterion would serve only to discourage reporting of bona fide cases of this condition.

## Case Report

Mrs. H. N., a 32-year-old nulliparous Negro woman, was admitted to the gynecologic service at Michael Reese Hospital March 13, 1954, because of menorrhagia of 9 months' duration and multiple fibroids of the uterus the size of a 24 weeks' gestation. Pelvic examination confirmed this, but on rectovaginal examination a hard tender nodular projection was found behind the cervix. A subtotal hysterectomy was performed because the bladder was very adherent to the uterus, the dome of the bladder being denuded during the procedure. The pathology report revealed multiple uterine myomas with secondary changes, and proliferative endometrium.

The patient did not return for follow-up examination until June, 1957, when she complained of severe low back pain of 9 months' duration, and cyclic vaginal bleeding for the previous 4 months varying from a scant to heavy flow and lasting up to a maximum of a week. Speculum examination showed a normal-appearing cervix and a nodular ulcerated mass in the posterior fornix behind the cervix. Rectovaginal and abdominal examination revealed two masses: one a 3 by 5 cm. hard, fixed mass in the rectovaginal septum, and a second mass 8 cm. in diameter, cystic, and attached to the top of the cervix. Biopsy of the vaginal mass disclosed markedly hyperplastic stratified squamous epithelium with underlying papilliferous glandular structures in fibrous stroma, suspicious of adenocarcinoma. The patient was admitted to the hospital for further workup and treatment on July 22, 1957.

<sup>\*</sup>Presented at a meeting of the Chicago Gynecological Society, Feb. 21, 1958.

Physical examination showed an obese 35-year-old woman with a blood pressure on admission of 200/120. Repeat Papanicolaou smears were positive and biopsy of the posterior vaginal fornix showed papillary adenocarcinoma infiltrating the submucosa of the vagina. Endocervical biopsy revealed endocervical epithelium with atypical squamous metaplasia and a fragment of hyperplastic squamous epithelium. Proctoscopy showed normal rectal and sigmoid mucosa but an irregular bulging was present in the lower rectal wall. Cystoscopic



Fig. 1.—Ulceration of carcinoma in posterior wall of vagina.

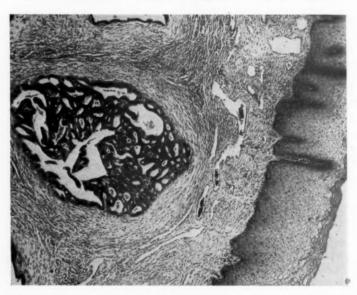


Fig. 2.—Carcinoma infiltrating stroma beneath vaginal mucosa. (Hematoxylin and eosin stain.  $\times 300$ ; reduced  $\frac{1}{6}$ .)

examination was normal. Funduscopic examination revealed early hypertensive changes. Upper and lower gastrointestinal roentgen studies were normal. Intravenous pyelography showed a mass pressing on the bladder roof. Chest films and electrocardiograms were normal. It was decided that a combined gynecologic and surgical team perform a laparotomy on this patient. The patient's bowel was prepared by oral administration of Chloromycetin.

Through a left lower abdominal paramedian incision exploration of the abdomen disclosed the liver, small bowel, and colon to be normal. No enlarged aortic lymph nodes could be palpated. A cystic 5 cm. mass was adherent to the top of the cervix, the bladder, the

Fig. 3.

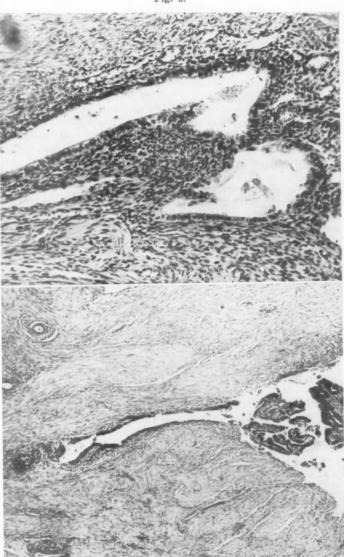


Fig. 4.

Fig. 3.—Area of definite endometriosis. (Hematoxylin and eosin stain.  $\times 600$ ; reduced %.)

Fig. 4.—Area of endometriosis showing apparent transition to carcinoma. (Hematoxylin and eosin stain.  $\times 300$ ; reduced %.)

uterosacral ligaments, and both tubes. The infundibulopelvic ligaments were clamped and cut, the iliac vessels and ureter were exposed, revealing no enlarged lymph nodes. The cervix and vagina were separated from the bladder. A hard 3 by 5 cm. nodular mass was present

in the rectovaginal septum, firmly adherent to both the rectum and vagina. An abdominoperineal excision of the sigmoid colon, cervix, and all of the vagina except for a 1 cm. strip beneath the terminal urethra, was performed.

Gross examination of the pathologic specimen, aside from Fallopian tubes and one attached 5 cm. simple ovarian cyst, revealed a segment of anorectosigmoid colon measuring 14 cm. in length by 5 cm. in circumference, a stump of cervix measuring 3.5 cm. in length and 2.5 cm. in diameter, and a portion of vaginal mucosa measuring 10 by 6 cm. (Fig. 1). Beginning 1 cm, below the cervix and attached firmly to the vaginal mucosa over an ulcerated area measuring 2 by 2 cm., was a grayish-white, stony-hard, irregular mass measuring 3.5 by 3 by 2.5 cm., which infiltrated the surrounding structures in the form of grayish-white radiating streaks of tissue. On sectioning, the mass was grayish white and contained occasional bluish minute punctate areas which could best be seen on the vaginal mucosal surface. The mass infiltrated the uppermost outer portion of the posterior cervical wall, but the cervical mucosa appeared uninvolved. The tumor also appeared firmly attached to the perirectal fibrofatty tissue, but the wall and mucosa were grossly not involved. In the mid-portion of the segment of rectum, however, was an area of flat mucosal folds measuring 4.5 by 3.5 cm., corresponding roughly to the region of the tumor attached to its outer surface.

Hematoxylin and eosin stained microscopic sections of the tumor revealed nests and masses of hyperchromatic columnar malignant cells forming cysts and glandular structures in a dense fibrous stroma. Many mitotic figures were present. These features were typical of a well-differentiated papillary cystadenocarcinoma (Fig. 2). Intermingled with the neoplastic structures were outspoken endometrial glands surrounded by endometrial stroma. In one region there seemed to be almost a transition between the endometrial areas and the tumor areas (Figs. 3 and 4).

In retrospect, the history of cyclic bleeding from the vaginal mass was an important clinical point in suggesting the possibility of an endometriosis process together with the carcinoma.

# Summary

A case of adenocarcinoma probably arising from endometriosis of the rectovaginal septum is reported together with a brief review of the literature.

Addendum.—Shortly after this report was submitted, 2 additional cases of carcinoma arising in endometriosis were reported by Ferreira and Clayton.23

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# Obstetrics

# HEMOGLOBIN CHANGES IN LABOR AND THE PUERPERIUM

A Study of 102 Patients

JO MILLER, M.Sc., M.D., H. B. WILLIAMS, M.D., AND J. L. MACARTHUR, F.R.C.S. (C), MONTREAL, QUEBEC

(From the Montreal General Hospital)

THE object of this study is to record the changes in the level of hemoglobin in the maternal blood during the course of labor, delivery, and the early puerperium, and to attempt to correlate these changes with various environmental and individual factors. It is hoped that the results of this work, in conjunction with preceding and subsequent work of other investigators, might increase the general knowledge of the changes in the composition of blood in pregnancy, help to anticipate the abnormal in any group of apparently normal cases, and, finally, establish the earliest satisfactory time in which routine postpartum hemoglobin studies could be made.

In any normal pregnancy, certain variable factors are known to influence the composition of the blood during labor, the sum of all these determining the peripheral values at any one time in any one patient. The hemoglobin concentration is decreased by the well-known hydremia of pregnancy which produces an apparent anemia, 1, 2, 3 and in the puerperium by dilution of blood due to the transfer of tissue fluids into the circulation to replace the variable but inevitable loss of blood at delivery. In contrast, tending to raise the hemoglobin level by hemoconcentration, dehydration may occur during labor when fluid intake is decreased and insensible fluid loss increased with the efforts of labor. In addition, the diuresis of the puerperium is said to occur, further concentrating the blood and raising the hemoglobin level.

The factors are largely independent of one another and their interaction may mask a significant loss of blood, producing a normal hemoglobin value in the presence of a reduced circulating total, or, on the other hand, may give rise to a value indicating a considerable degree of anemia when actually there is a total mass of hemoglobin above the normal, thinly distributed in a large circulating volume.

Nowhere in the literature could there be found results of the type of study undertaken here, that is, a large series of short-interval hemoglobin determinations taken under standard research conditions and covering the period from early labor until discharge from the hospital. To assess accurately the changing character of the circulating substance, simultaneous volume studies would be advantageous. These were not undertaken, however, because the technical problems associated with multiple determinations of this nature, often at short intervals, exceed the limit of the project.

## Review of the Literature

In the healthy nonpregnant individual, the hemoglobin level varies with the time of day,4 bed rest,5 meals,6 and the season.7 There is little variation with age between the years of 18 and 60.8 There is no evidence in the literature which might indicate that these changes do not apply in pregnancy and the puerperium.

The changes in the blood associated with pregnancy embrace many of its elements. The literature is massive and often contradictory but has been competently and exhaustively reviewed recently by Tysoe and Lowenstein.1 They noted in summary of these previous works that the hemoglobin concentration level progressively falls during the course of pregnancy to a minimum in the last trimester, then rises slightly to term. The total hemoglobin increases throughout pregnancy and the apparent progressive anemia is due to an expanding total blood volume parallel to and slightly more extreme than the hemoglobin changes. Eastman suggested that the normal range in pregnant women is identical with that in nonpregnant women, that is, 12 to 15 Gm. per cent, and that a value of below 12 Gm. per cent is pathognomonic of an iron deficiency state, while Bethell<sup>10</sup> termed 11.3 Gm. per cent as the lowest level explainable by the physiological hydremia, and others<sup>3, 11</sup> have quoted even lower figures.

The changes associated with actual labor, delivery, and the early puerperium are not reported as voluminously as are the antepartum changes and only a few works contain the results of careful serial determinations at short intervals during and after labor. Dieckmann and Wegner<sup>12</sup> found that results of studies in the first 24 hours post partum are characterized by irregular variations. In some of their cases in which serial determinations were made during labor and the early puerperium, there was a rise in the hemoglobin concentration during labor, a return in the first postpartum hour to the prelabor level, and then, irregularly, a slow increase during the next few days. Expressed simply, there was almost always, concurrently with labor, a transient increase in hemoglobin concentration. The authors did not comment on this phenomenon. Other authors<sup>2</sup> illustrated in tables of results an almost consistent increase in the hemoglobin concentration during labor, averaging 0.7 Gm. per cent, a subsequent fall to below antepartum levels on the fourth day, and then a slow irregular rise over the next several days. Average values in the first few days post partum are variously recorded as 12.1, 12 11.85, 13 11.3, 1 and 12.2 to 13.0 Gm. per cent. 2

#### Method

Investigation was carried out on 102 patients consecutively admitted to the obstetrical unit of the Montreal General Hospital. All patients were representative of better than average economic conditions and all were privately managed by the attending staff, all in a similar manner. Cases characterized by prematurity, toxemia, and multiple pregnancies were excluded. There was no instance of placenta previa, abruptio placentae, or blood dyscrasia. Prematurity was considered to be present in cases of less than 36 weeks' gestation or those in which the weight of the newborn infant was below 2,500 grams, the latter being the conclusive evidence in conflicting cases. In some cases the hospital stay was shorter than in others, and, infrequently, determinations were missed because of unavoidable circumstances. The usefulness of the records of these cases was limited by their incompleteness.

Hemoglobin determinations were made on each patient as soon as possible after the beginning of labor, again within an hour after delivery, and repeated on each day following between the hours of 7 and 9 a.m. for the rest of the hospital stay. The first postpartum day was considered to be the day of delivery if the delivery occurred before noon, but the day following if it occurred after noon.

Technique.—All technical planning and procedure were done by two of the authors. Each patient was followed throughout her investigation by the same author, who did, with only rare exceptions, all the work associated with that patient. Throughout the investigation, pipettes and tubes were numbered and the same ones retained for the entire study of any one patient, thereby eliminating the compounding of instrument error. Capillary blood for determinations was obtained by the finger prick method as outlined by Whitby and Britton.<sup>8</sup>

The various methods of determination were reviewed<sup>8</sup> and the acid hematin method adopted, since it has the advantages of being simple and accurate and of being adaptable to photoelectric colorimetry. The photoelectric colorimeter used was standardized by comparative determinations with a Van Slyke apparatus with the oxygen uptake method. A graph was evolved to transcribe colorimeter reading to values in grams of hemoglobin per 100 ml. of blood.

For each determination, 0.05 ml. of capillary blood was drawn into a standard measuring pipette and then discharged into and thoroughly mixed with 25 ml. of N/10 HCl contained in a special photoelectric colorimeter tube. After the acid hematin was allowed to develop for at least 45 minutes, this unknown was compared with a standard in a photoelectric colorimeter. The light transmission interference was recorded and transcribed into a value indicating the hemoglobin concentration.

#### Results

Error.—An effort was made to determine the inherent error of the equipment used and the variation associated with technique. The range of results was established for groups of ten determinations, each group devoted to one variable, such as pipettes, colorimeter tubes, sampling by the finger prick method, and the technique characteristics of the two authors. From this was derived a range within which any ten determinations might be expected to vary as a result of these characteristics of equipment and technique. That range was found to be  $\pm$  0.26 Gm. per cent.

While the results were not evaluated by statistical analysis, it is felt that they are an indication of the tendencies of the values to change in certain directions and to certain degrees in response to the related conditions.

Hemoglobin at Term.—The average value of hemoglobin concentrations in early labor was 12.8 Gm. per cent, with results ranging from 10.3 to 14.4 Gm. per cent. This average falls well above the minimum normal values.<sup>9, 10</sup>

Parity was found not to affect the term hemoglobin, the average values of the various parity groups being identical (Table I). Hemoglobin at term varied irregularly with age (Table II) but there was some support for the supposition that the older pregnant woman is more prone to develop anemia than is her younger sister.<sup>14, 15</sup>

TABLE I. HEMOGLOBIN CONCENTRATION AT TERM AND ITS RELATION TO PARITY

PARITY	NO. OF PATIENTS	AVERAGE HEMOGLOBIN (GM./100 c.c.)
0	50	12.8
i	20	12.8
ii	13	12.9
iii	6	12.8
Total	89	12.8

TABLE II. HEMOGLOBIN CONCENTRATION AT TERM AND ITS RELATION TO AGE

AGE GROUP	NO. OF PATIENTS	AVERAGE HEMOGLOBIN (GM./100 c.c.)
20-24	19	12.8
25-29	35	12.7
30-34	22	13.3
35+	13	12.4
Total	89	12.8

# Hemoglobin Changes in Labor and the Puerperium.—

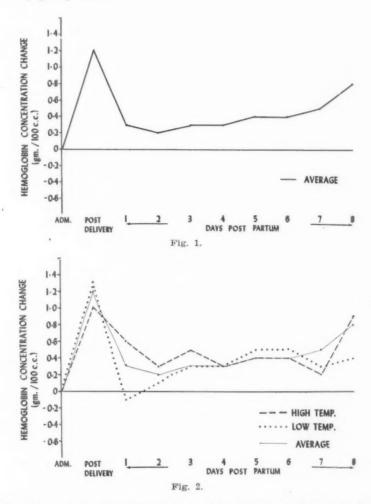
1. General considerations: The average values of hemoglobin concentration for the series (Fig. 1) show a marked increase during labor followed by a return almost to the antepartum level on the first day after delivery. This value was maintained for 4 days and was followed by a slow increase until, on the eighth postpartum day, the hemoglobin concentration was 0.8 Gm. per cent greater than it was at term.

Of 76 patients studied during labor, the vast majority, 71, showed an increase in the hemoglobin concentration, 3 showed no change and only 2 a decrease. Even in cases in which the duration of labor and delivery was exceedingly short, an increase in hemoglobin concentration was the rule rather than the exception. The average change in all these cases was a rise in the hemoglobin concentration of 1.2 Gm. per cent. In all the literature reviewed, only two studies<sup>2, 12</sup> demonstrated evidence of similar observations, in both instances recorded in graphs or tables but without related comment in the text. The causes of this change are considered in the discussion.

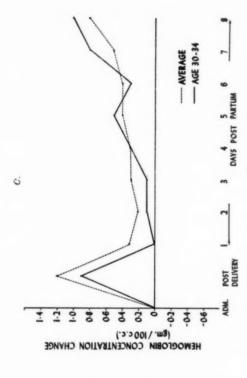
During the puerperium, the range of changes in individual cases was considerable. The greatest increase above the term level amounted to 3.9 Gm. per cent, and the greatest decrease was 4.0 Gm. per cent. These was no obvious explanation for these extreme changes.

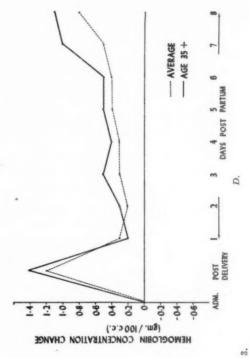
2. The effect of temperature: To study the effect of atmospheric temperature on hemoglobin changes, two groups of patients were selected and the average values compared, one group having labored and been delivered in

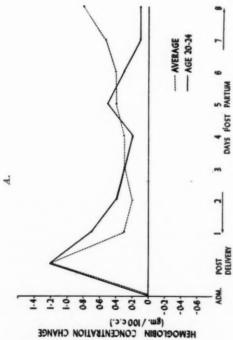
weather relatively warmer than that of the other group, the average mean temperatures being 79 and 68° F., respectively. The results (Fig. 2) show that changes in hemoglobin concentration during labor are not greatly affected by atmospheric temperature but that there is clearly a different response in the very early puerperium.

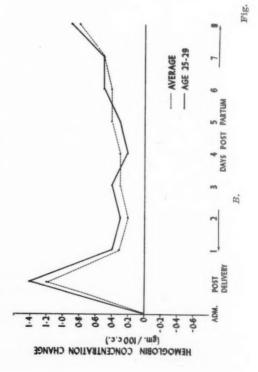


- 3. The effect of the length of labor: The degree of change in hemoglobin concentration in labor was compared with the duration of labor in 70 cases (Table III). It was found that when the duration of labor was less than 2 hours, the increase in the hemoglobin concentration was only slightly less than in the cases with a more prolonged labor. There was no regular relationship between the degree of change and the length of labor.
- 4. Effect of age and parity: Comparison of hemoglobin concentration changes with the age and the parity of the patient revealed that during labor small irregular differences occurred. In the early puerperium (Fig. 3), the youngest age group is characterized by hemoglobin values somewhat above the average in the first few postpartum days in contrast to a below-average









value for the oldest age group during the same period. On the seventh and eighth days, the situation is reversed with the value of the youngest age group lying well below the average, and the older age groups being distributed at regular intervals upward.

TABLE III. CHANGE IN HEMOGLOBIN DURING LABOR AND ITS RELATION TO DURATION OF LABOR

DURATION OF LABOR	NO. OF CASES	AVERAGE CHANGE (GM./100 C.C.)
Less than 2 hours	10	+0.9
2 to 6 hours	28	+1.2
3 to 12 hours	24	+1.4
Over 12 hours	8	+1.2
Fotal	70	+1.2

5. The effect of blood loss at delivery: The changes in hemoglobin concentration were compared with the amount of blood lost at delivery. The quantity lost was estimated at the end of each delivery, based on the experience gained in actual measurements, and was expressed as one of three grades, the higher grades referring to more extensive losses. The results (Fig. 4) show that changes in hemoglobin concentration during the period of delivery are identical in spite of the variation in the degree of bleeding. In the puerperium, however, there is an obviously marked decrease in the average hemoglobin concentration in the cases in which the blood loss at delivery was more extreme. These changes are probably due to a sudden decrease in the maternal circulating volume at delivery, and its subsequent reconstitution and dilution by a shift of interstitial fluids into the vascular tree. These changes are not reflected in the postdelivery hemoglobin determination, but become obvious in the next determination some hours later when they are more advanced. From the third to the eighth postpartum day, there is a return to the antepartum level, possibly the result of a fluid shift opposite to the original one or of a rapid erythropoiesis.

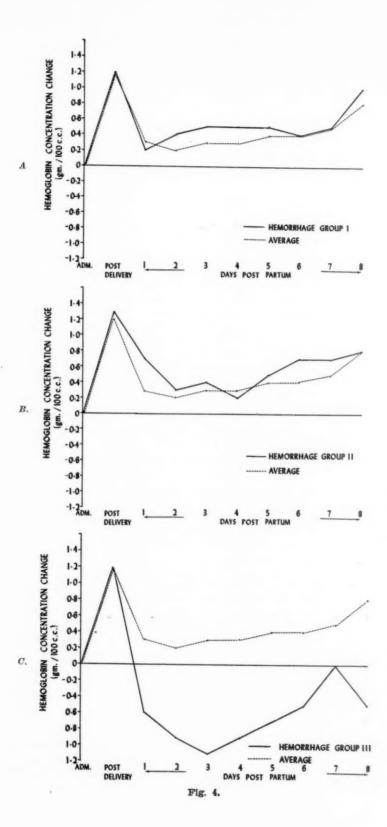
Stabilization of the Blood and Routine Hemoglobin Studies.—It appeared desirable to establish the time at which the blood picture in the puerperium became stabilized to such a degree that no further sudden or extensive change might be expected. With this information, routine postpartum studies could be scheduled as early as possible to obtain a value representative of a

relatively constant blood composition.

It was found that if the routine study had been done on the first day 15 per cent of the cases would have been characterized by a drop in hemoglobin concentration of 1.0 Gm. per cent or more during the subsequent hospital stay. If the routine study had been done on the second day, 17 per cent of the cases would have shown this range, and if on the third day, 12 per cent. If the routine study had been done on the fourth or fifth day, however, only 5 per cent of all the cases would have been characterized in the subsequent hospital days by a range downward of 1.0 Gm. per cent or more. This means that a routine study done on the fourth or fifth day yields results which in 95 per cent of cases represent a value below which the hemoglobin concentration will not fall to any degree.

#### Comment

The almost inevitable transient increase in hemoglobin concentration noted during labor and delivery has not been commented on previously in the literature, although the records of other investigators show that the phenomenon has been detected. Several possible explanations of this interesting



change can be considered. The loss of blood at delivery does not appear to be responsible (Fig. 4). The so-called diuresis of the puerperium, not widely mentioned in recent literature, probably could not produce such a sudden change, since about 500 ml. of fluid would have to be removed from the circulation without replacement to produce an increase in the hemoglobin concentration of 1 Gm. per cent. There might occur a shift of fluid from the vascular to the interstitial spaces in response to the stress of the occasion, the process being reversed in the few hours following delivery.

Nowhere in the literature has the insensible loss of fluid by perspiration during labor been considered as significantly affecting the circulating volume. It is not unusual, however, to see, anywhere in the world, a woman straining with the effort of her labor, perspiring freely, her hair matted, the bed sheets dampened. Where does this fluid come from? How much is lost? Best and Taylor¹c claim that up to a liter of fluid can be lost in a single hour under extreme circumstances. What is the effect on the circulation of this loss? Perhaps this sudden effusion is responsible for the rapid hemoconcentration detected here, and also for the puzzling loss of circulating volume detected by others.²

If, indeed, this increase in hemoglobin concentration is due to fluid lost by perspiration, then the degree of increase should vary with the length of labor and with the temperature of the environment in which the patient labored.

The results of studies related to the length of labor show that, in very short labors, the increase is less marked than in longer labors (Table III). The results of studies relating the degree of change to atmospheric temperature (Fig. 2) did not support this proposition. Hemoglobin concentration changes in groups of patients under different conditions were almost identical. On the first postpartum day, however, when the average values decreased toward the antepartum level, probably as a result of a shift of interstitial fluid into the circulation to replace the blood lost at delivery, a marked difference was noted between the groups which were delivered under different condi-The warm weather group remained in a state of relatively greater hemoconcentration. This may be attributed to a greater insensible loss of fluid in warm weather depleting the interstitial fluid reserves available to reconstitute the circulating volume. By the second postpartum day, however, when in the normal course of events or lintake re-establishes the body fluid reserve, the values of the two groups approach one another and thereafter are almost identical.

The change in hemoglobin concentration in the puerperium appears to be regularly related to the age of the patient (Fig. 3), but there is no ap-

parent explanation for this.

On and after the fourth postpartum day, the blood pictures of 95 per cent of the patients were characterized by either stable or increasing hemoglobin concentrations. In only 5 per cent of the studies was there exhibited a decreasing concentration with a range of 1.0 Gm. per cent or greater. Therefore, the earliest effective time for routine postpartum hemoglobin studies appears to be on the fourth day, this being sufficiently early to satisfy the clinical curiosity of the obstetrician and yet late enough so that, in most instances, the hemoglobin concentration is relatively stable or is rising. The results of a determination done on the fourth day can be read with the knowledge that in almost every case the hemoglobin concentration will neither be subject to gross changes nor show a tendency to decrease more than a trace in the subsequent few days.

# Summary and Conclusions

1. Serial hemoglobin determinations were made in a large number of cases during labor and the early puerperium and the results are presented.

2. The average hemoglobin concentration at term was 12.8 Gm. per cent.

3. Parity had no effect on the hemoglobin at term.

4. Age and hemoglobin at term were irregularly related, with a tendency toward anemia in the older groups.

5. The hemoglobin concentration increased in almost every case during the course of labor, the average increase in all cases being 1.2 Gm. per cent. The possible physiological mechanisms responsible for this change are discussed and include a sudden shift in circulating fluids into the interstitial space, or a progressive hemoconcentration due to increased fluid loss by perspiration during the efforts of labor.

6. Warmer atmospheric temperature was found to have little effect on the change of hemoglobin concentration during labor, but clearly impaired the return of values to the antepartum level, probably because of a depletion in interstitial fluid reserves by a heavier insensible loss. This in turn prevented the complete reconstitution of the circulating volume which had been reduced by the blood loss at delivery. Therefore, in labors conducted in very warm or humid weather, particularly where labor is long, where the loss of fluid might be extensive, intravenous therapy may be indicated.

7. The increase in hemoglobin concentration was less marked in very short labors.

8. There was little relation between the increase in hemoglobin concentration in labor and the age and parity of the patient.

9. The average changes in hemoglobin concentration in the puerperium varied regularly with the age of the patient.

10. There is a clear relation between the amount of intrapartum blood loss and the subsequent changes in hemoglobin concentration.

11. The earliest satisfactory time for routine postpartum hemoglobin studies is the fourth day.

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# MEASUREMENT OF UTERINE BLOOD FLOW AND UTERINE METABOLISM

VI. Effects of Oxytocic, Vasopressor, and Vasodepressor Drugs on the Blood Flow to the Postpartum Uterus in Unanesthetized Sheep\*

N. S. Assali, K. Dasgupta, and A. Kolin, Los Angeles, Calif.

(From the Departments of Obstetrics and Gynecology and Biophysics, University of California, School of Medicine)

In A previous report¹ we presented data on the effects of spontaneous and oxytocin-induced labor as well as the effects of postpartum uterine involution on uterine blood flow as measured with the electromagnetic flowmeter in unanesthetized pregnant dogs and sheep. It was shown that uterine contraction, regardless, of whether it resulted from spontaneous labor or from labor induced with oxytocin, was accompanied by a significant decrease in blood flow which was roughly proportional to the magnitude of the contraction. During uterine relaxation a reactive hyperemia-like phenomenon was observed during which the blood flow returned to, or was slightly higher than, control levels. Immediately after delivery of the fetus and placenta an initial and precipitous fall in uterine blood flow occurred. This was followed by a slower and more progressive decrease which roughly paralleled the involution of the uterus.

Since oxytocic drugs are commonly used as hemostatic agents in obstetrics in the postpartum period, the present study was intended to investigate their effects on uterine blood flow after delivery of the fetus and placenta. The studies also include data on the effects of epinephrine, norepinephrine, and hydralazine (Apresoline) on postpartum uterine blood flow.

#### Method

Uterine blood flow was measured with the electromagnetic flowmeter. Although details of the physical and instrumental characteristics of this method, as well as of the procedure for implanting the sensing unit around the uterine artery, have been outlined elsewhere, 1, 2 a brief description is given here.

The principle of the electromagnetic method for measuring flow of fluids is based on the electromagnetic induction discovered by Faraday. This phenomenon consists essentially of inducing an electromotive force (emf) in a closed electrical circuit traversed by a varying magnetic flux. In 1936, Kolin³ showed that electromagnetic induction can be used for quantitative measurements of flow of fluids in pipes and demonstrated the existence of a linear relationship between the volumetric rate of flow and the induced voltage. He

<sup>\*</sup>Supported by grants from the National Heart Institute, U. S. Public Health Service, The California Heart Association, and Parke, Davis & Company, Detroit, Mich.

further demonstrated that the flow of blood through arteries could be recorded by merely applying nonpolarizable electrodes to the outside of the walls of the artery at the ends of its diameter and perpendicular to the magnetic field. Various flowmeters were subsequently developed to measure regional blood flow in anesthetized as well as unanesthetized animals, the most recent of which is presented in Fig. 1. This flowmeter consists essentially of a magnet encapsulated in plastic material. A lucite sleeve, into which the vessel to be studied is placed, is inserted in the gap of the magnet. The whole unit is goldplated for insulation. The wires emerging from the magnet lead to the energizing as well as to the amplifying and recording systems. Flowmeter units of varying sleeve diameters are made for vessels of different sizes. The entire unit can be implanted chronically around the main vessel supplying the organ to be studied. In a short period of time, adhesions are formed between the flowmeter and the surrounding area. These adhesions fix the unit in a definite position, thus preventing alteration of the flowmeter position induced by movements of the animal. In this way, measurement can be made in conscious animals moving about as far as the length of the lead wires permit.

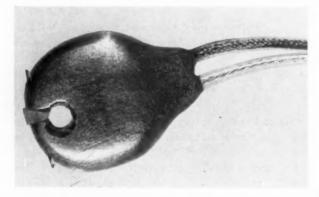


Fig. 1.—The miniature electromagnetic flowmeter for chronic implantation. Note the sleeve in which the vessel to be studied is placed. The T piece closing the upper pole of the sleeve can be removed to allow the vessel to be slipped into the channel and then the piece put back in its position in order to close the ring entirely. In this way the vessel cannot escape from the sleeve.

Besides the advantages of permitting circulatory studies in unanesthetized animals, the electromagnetic method for measuring flow gives the instantaneous blood flow with its systolic and diastolic components. Average blood flow can be obtained by either planimetry or by an electronic integrator incorporated into the circuit. It should be emphasized, however, that from the point of view of hemodynamics the changes in the diastolic and average flow are the most important since they reflect more closely the status of the arteriolar system.

Implantation of the flowmeter unit around the uterine artery in the pregnant sheep was made under a light barbiturate or spinal anesthesia. Using the transperitoneal or the extraperitoneal approach, one uterine artery was exposed close to its exit from the hypogastric artery. A 2 cm. segment was freed from its surrounding tissues and was slipped through a slit into the sleeve located in the gap of the magnet. The incision was closed, and a small opening was left through which the lead wires passed to the outside. These wires were kept attached to the skin of the back of the animal and were protected by an abdominal binder. The animal was allowed to recover from the effects of anesthesia before blood flow recordings were begun.

Three unanesthetized sheep were used in the present studies. In each animal the flowmeter was implanted before labor and delivery of the fetus. Postpartum recordings of uterine blood flow began in each animal on the first day after delivery of the fetus and placenta and continued for 10 to 14 days

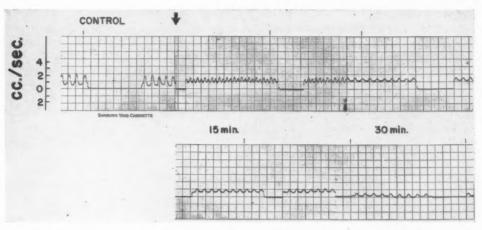


Fig. 2.—Effects of intravenous administration of Pitocin on the instantaneous blood flow to the uterus in the early postpartum period. In this and subsequent figures, only a small segment of the record is given and the zero base line was taken frequently in the control period and during the action of the drug in order to facilitate the reading of flow values. The arrow indicates the time of injection of 1 c.c. of the drug. Note the immediate tachycardia and initial increase in the diastolic flow, with alteration of the flow complex and slight decrease in the systolic flow. Later, the diastolic and systolic flow fell progressively and remained low for periods of 100 to 120 minutes.

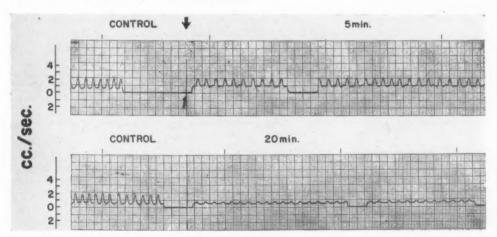


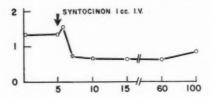
Fig. 3.—Effects of intramuscular injection of 1 c.c. of Pitocin on postpartum uterine blood flow. The upper segment of the record shows the negligible effects observed 5 to 10 minutes after the injection. The lower segment shows the marked reduction in both systolic and diastolic flow which was observed 15 to 20 minutes after the intramuscular injection. Segments of the control records are attached to facilitate comparison of effects. The arrow indicates the time of injection of the drug.

thereafter. During the daily recordings, the animal was either standing quietly eating its feed or was lying on a wooden board. No significant difference was observed in the values obtained in these two positions. Control measurements of uterine blood flow were obtained for about 30 to 45 minutes. Immediately thereafter, a known dose of the drug to be tested was injected

rapidly either into the jugular vein or intramuscularly and blood flow recordings were continued intermittently for 4 to 6 hours. A period of 8 to 12 hours was allowed for complete recovery from the effects of a drug before testing another drug or before testing the effects of another dose of the same drug.

#### Results

I. Effects of Oxytocic Drugs.\*—A total of 15 tests with Pitocin and Syntocinon and 8 tests with ergonovine were performed. Fig. 2 illustrates a typical example of the effects of the intravenous injection of Pitocin during the first week post partum. An initial and transitory rise in the diastolic and average flow occurred immediately after the injection and was followed by a marked and more persistent reduction in uterine blood flow. The systolic flow was reduced promptly after the injection of the drug and remained low until the



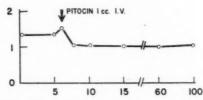


Fig. 4.—Effects of intravenous injections of 1 c.c. of the synthetic oxytocic fraction of the posterior pituitary hormone (Syntocinon) and of the natural fraction (Pitocin) on the average postpartum uterine blood flow in sheep. The average flow was obtained by planimetry of the original record and is given in cubic centimeters per second. Note the initial and transitory increase in blood flow which followed the injection of the drugs. A greater and more persistent decrease in blood flow followed and lasted for 100 to 120 minutes. The difference in the magnitude of fall in blood flow between the 2 preparations was not significant.

effects had subsided. A similar pattern was observed after intramuscular administration of the drug except that the onset of action was more delayed (Fig. 3). The action of Syntocinon was closely similar to that of Pitocin, both in intensity and duration (Fig. 4). The effects of intravenous injections lasted for 100 to 120 minutes, whereas those of intramuscular injections lasted for 180 to 220 minutes. Table I shows the effects of the intravenous injection of 1 c.c. of oxytocins on uterine blood flow on different days post partum. The control flow values decreased progressively from the first to the tenth day. A single intravenous dose evoked a 45 to 50 per cent reduction in blood flow on the first postpartum day, 40 per cent on the fifth day, and 25 per cent on the tenth day (Table I). Only doses of 1 c.c. and 2 c.c. were tested and the difference in their action was not significant. These drugs produced in the unanesthetized sheep a tachycardia which varied in intensity from one animal to another.

<sup>\*</sup>The oxytocic drugs utilized in these studies were: Syntocinon (synthetic posterior pituitary hormone, 10 I.U. per cubic centimeter), Pitocin (natural hormone, 10 I.U. per cubic centimeter), and Methergine (methylergonovine maleate, 0.20 mg. per cubic centimeter),

The effects of ergonovine on uterine blood flow were closely similar to those of Pitocin and Syntocinon except that the initial and transitory increase in flow, which occurred invariably after the latter drugs, was not observed after ergonovine (Fig. 5). The action of ergonovine also decreased progressively during the postpartum period and on the tenth day it was negligible (Table I). Ergonovine did not materially change the heart rate (Fig. 5).

II. Effect of Epinephrine and Norepinephrine.\*—A total of 14 tests were performed with epinephrine and norepinephrine in the postpartum period. Intravenous injection of epinephrine in doses of 1 to 2 c.c. did not change significantly the average postpartum uterine blood flow (Fig. 6). The flow complex, however, showed some alteration which consisted of the slowing of the heart rate with a slight systolic fall and a diastolic rise (Fig. 6). No significant difference was observed between the effects of 1 and 2 c.c.

The intravenous injection of norepinephrine in doses of 1 to 2 c.c. produced an immediate tachycardia with a reduction in the systolic flow (Fig. 7). The diastolic flow increased for the first 3 to 5 minutes but then began

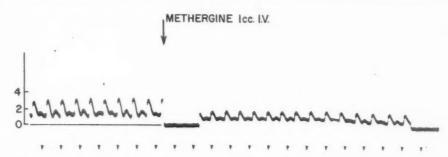


Fig. 5.—Effects of intravenous injection of 1 c.c. of ergonovine (Methergine) on the instantaneous blood flow to the postpartum uterus. For space economy, only small segments of the control and postinjection records are given. Note the marked fall in the over-all flow after the injection of the drug. Ergonovine, unlike Pitocin and Syntocinon, did not produce an initial rise in the postpartum uterine blood flow. The duration of action of ergonovine was not different from that of the posterior pituitary hormone. The heart rate remained unchanged after the administration of ergonovine.

to return to or below control levels (Fig. 7). These effects lasted for periods varying from 45 to 60 minutes. Here again, the effects of 1 c.c. were not different from those of 2 c.c.

Table I. Effects of Intravenous Injection of 1 c.c. of Pitocin and 1 c.c. of Ergonovine on Average Uterine Blood Flow on Different Postpartum Days

			DD FLOW ETERS PER SECOND)
DRUG	DAYS POST PARTUM	CONTROL	MAXIMUM DRUG EFFECT
Oxytocin	1	1.3	0.7
	5	1.0	0.6
	10	0.8	0.6
Methergine	1	1.4	0.7
	5	0.9	0.6
	10	0.7	0.6

\*The values listed under maximum drug effect refer to the lowest readings observed after the injection of the drugs.

\*The epinephrine preparation utilized was Adrenalin chloride solution 1:1,000, and the norepinephrine was Levophed bitartrate solution, 0.2 per cent.

III. Effects of Apresoline.—Seven tests were performed with intravenous injections of Apresoline. This drug in doses of 20 to 40 mg. evoked a consistent rise in the average uterine blood flow which became evident 4 to 5 minutes after the injection and lasted for 5 to 6 hours (Figs. 8 and 9). The

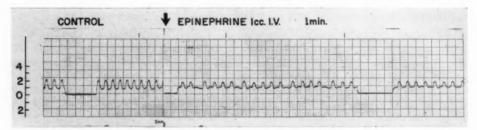


Fig. 6.—Effects of intravenous injection of 1 c.c. of epinephrine on the instantaneous uterine blood flow. Note that with the exception of slowing of the heart rate and a slight modification in the flow complex, the systolic and diastolic flows remained practically the same. The effects of 2 c.c. were similar to those of 1 c.c.

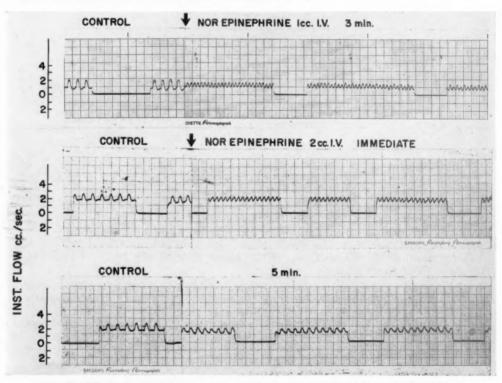


Fig. 7.—Effects of the injection of 1 and 2 c.c. of norepinephrine intravenously on the instantaneous uterine blood flow. Note the tachycardia and the change in flow complex with disappearance of the systolic peak. Note also the initial increase in the diastolic flow which is evident after both the 1 and the 2 c.c. doses. Five to 10 minutes after the injection, the diastolic flow began to return to control values or below. Segments of the control records are attached to each record of drug action to facilitate comparison of flow values.

rise was mainly due to a marked increase in the diastolic flow (Fig. 8). The systolic peak of the flow complex nearly disappeared, giving the aspect of a flat complex. Tachycardia appeared invariably 5 to 7 minutes after the injection of Apresoline.

#### Comment

Oxytocic drugs in the form of posterior pituitary extracts or purified hormones and in the form of ergot preparations have been used somewhat empirically for many years in obstetrics in order to produce postpartum hemostasis and hasten the involution of the uterus through uterine muscle contraction. However, knowledge of the exact mechanisms of the action of these drugs is lacking since their effects on the uterus are complex and many features are still controversial.

It is a general belief that the responsiveness of the uterus to posterior pituitary hormones varies according to the stage of pregnancy and from one animal to another.<sup>4</sup> It is minimal during early gestation and gradually increases until term and immediately post partum. It has also been suggested that the nonpregnant uterus is more responsive to the pressor pituitary hormone than to the oxytocic fraction whereas the opposite occurs in the case of the pregnant or early postpartum uterus.

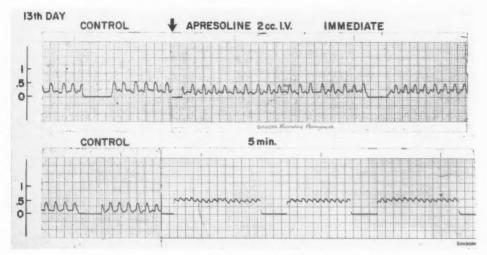


Fig. 8.—Record of the instantaneous blood flow to the uterus on the thirteenth post-partum day, before and after the injection of Apresoline. Note that the control blood flow had decreased markedly from the levels observed in the first few days after delivery. Nevertheless, a marked increase in the diastolic flow with a concomittant tachycardia and a fall in the systolic flow is observed 5 minutes after the injection of the drug. The flow complex is altogether changed.

The circulatory effects of oxytocin are likewise confusing, mainly because of marked species differences. Woodbury and his co-workers, 6, 7 have noted that the injection of 3 units of oxytocin into pregnant human subjects produces a transient hypotensive action together with an increased force of uterine contraction. They believe that the hypotension is probably due to a transient myocardial depression caused by the drug. Because of the hypotension and the increased uterine contraction, the effective maternal placental pressure calculated from the difference between the pressure developed by the uterus and the maternal arterial pressure falls thereby jeopardizing the placental circulation and hence the fetus. A similar fall in pressure and weakening of myocardial contraction were observed in the rabbit and cat but not in the normal dog. Although these authors did not measure uterine blood flow, their reasoning implies that the flow probably falls.

Our data on the effects of the posterior pituitary hormones on the blood flow to the postpartum uterus in the unanesthetized sheep showed two phasic responses. The first consisted of an initial and transitory rise and the second was a more persistent fall. It is difficult to explain both of these phases without simultaneous measurement of uterine force, arterial pressure, vascular resistance, and cardiac output. Nevertheless, two possibilities offer themselves to explain the second phase, which is the more significant. The first hypothesis is that the fall in uterine blood flow was due to a systemic effect of these drugs in terms of a transient myocardial depression and a possible fall in the cardiac output consonant with Woodbury's findings. This possibility seems unlikely since the reduced flow to the uterus after either the intramuscular or the intravenous injection was not transitory as mentioned by Woodbury but remained for a long period of time. Under these circumstances, it is difficult to visualize a myocardial damage with a reduced cardiac output and uterine flow for such a length of time without any evidence of systemic circulatory collapse since the animals appeared to be perfectly healthy. Furthermore, the effects of ergonovine on uterine blood flow were closely parallel to those of posterior pituitary hormones with the exception of the initial rise.

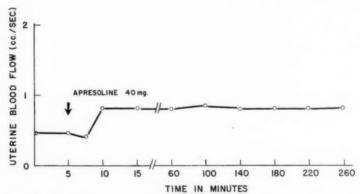


Fig. 9.—Average postpartum uterine blood flow obtained before and after the intravenous injection of 40 mg. of Apresoline on the thirteenth postpartum day. On that day, the flow had decreased considerably from the values obtained in the early postpartum period. Nevertheless, a marked and persistent increase in flow occurred approximately 5 minutes after injection of the drug and remained for several hours.

Although certain ergot alkaloids have a complex cardiovascular action, ergonovine is known to have the least effect on the systemic circulation and, therefore, neither its action on uterine blood flow nor that of the posterior pituitary hormones is likely to be due to a systemic circulatory effect.

The other alternative is that the decrease in uterine blood flow induced by these drugs is due to local action on the uterine blood vessels. This action could be mediated by either direct local vasoconstriction or by a mechanical constriction of the vessels produced by the contracting uterine musculature. This last possibility is supported by our observations and those of others which showed that uterine contraction during pregnancy produces a decrease and uterine relaxation an increase in uterine blood flow. Also, the fact that the effects of these drugs seem to decrease with the progressive involution of the uterus is consonant with the hypothesis that their action on uterine blood flow is local rather than systemic.

The action of epinephrine on the pregnant and nonpregnant uterus is variable and depends on the animal and dose employed. It is stated that in the sheep, the response of uterine musculature in the nonpregnant state is opposite to that of the pregnant state. However, most of these studies were limited to the action of the drug on muscle contraction. The present data

show that epinephrine in the dose employed did not significantly alter the postpartum uterine blood flow and induced a bradycardia instead of the usual tachycardia characteristic of this drug. Whether doses different from those employed here might have produced different responses cannot be stated from these studies.

On the other hand, norepinephrine which usually produces bradycardia evoked tachycardia in these animals with an initial rise in the diastolic and average blood flow. Such an increase in flow after the administration of norepinephrine is known to occur in the coronary circulation and it is possible that the uterine vessels respond to this drug in a manner similar to that of the coronary vessels.

The effects of Apresoline on uterine circulation were typical of the overall action of this drug, namely, an increase in heart rate and blood flow, the latter due to arteriolar vasodilatation. Such action has been observed to occur in the kidneys and brain.9

# Summary and Conclusions

- 1. The effects of oxytocic drugs and of epinephrine, norepinephrine, and Apresoline on the postpartum uterine blood flow were investigated in 3 unanesthetized sheep by the use of a chronically implanted electromagnetic flowmeter.
- 2. Natural and synthetic oxytocic fractions of the posterior pituitary produced an initial and transitory rise followed by a more persistent fall in uterine blood flow. Ergonovine produced a similar effect except for the initial rise.
- 3. It is postulated that the fall in blood flow is due to a local action in the uterus rather than to a systemic circulatory effect of these drugs.
- 4. Epinephrine produced no significant change in uterine blood flow and induced a bradycardia instead of tachycardia.
- 5. Norepinephrine raised initially the diastolic and average blood flow and evoked tachycardia instead of the usual bradycardia.
- 6. Appresoline produced a typical tachycardia and an increase in uterine blood flow.

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## THE PROBLEM OF SPONTANEOUS ABORTION

VI. Serum Seromucoid, Hexose, and Hexosamine in Spontaneous Abortion and Rheumatoid Arthritis\*

J. D. GRAY, M.D., HALIFAX, NOVA SCOTIA

(From the Department of Pathology, Halifax Infirmary)

THE presence of increased amounts of sensitized sheep cell agglutinating factor in the sera of aborting women¹ suggested the necessity of examining the blood of such patients for glycoprotein and seromucoid contents. It has been established that the serum concentration of these substances is often increased in the so-called collagen diseases.²

#### Materials and Methods

Serum from nonpregnant healthy women, from women in the first trimester of pregnancy, and women at term was obtained, and the hexose, hexosamine, and seromucoid content estimated in each. The results have been contrasted with those of a similar examination taken at the time of a spontaneous abortion and from patients known to have rheumatoid arthritis, the latter of both sexes.

Hexose, hexosamine and seromucoid were measured by methods suggested by Robinson and Roseman.<sup>2</sup> The Rose-Waaler titer was estimated in the case of spontaneous abortion and rheumatoid arthritis by the technique previously described.<sup>1</sup>

#### Results

## 1. Hexose Values in the Terms of Mean .-

25	nonpregnant healthy women	=	138	mg.	%	(S.D.	= 3.	7)
10	women at 3 months' pregnancy	=	143.7	mg.	%			

25 women at term = 157.9 mg. %

25 cases of abortion = 177.2 mg. % = 189 mg. %

Table I shows a comparison between the Rose-Waaler titers and serum hexose.

TABLE I. RELATIONSHIP BETWEEN ROSE-WAALER TITERS AND SERUM HEXOSE CONTENT

			RO	SE-WAAL	ER TITERS			
	1/1	16	1/3	2	1/0	34	1/128 ANI	ABOVE
	HEXOSE (MG. %)	NO. OF CASES	HEXOSE (MG. %)	NO. OF CASES	HEXOSE (MG. %)	NO. OF CASES	HEXOSE (MG. %)	NO. OF CASES
Abortion Rheumatoid	186	9	178	6	172	8	161	2 *
arthritis	182	6	187	5	188	9	209	3

<sup>\*</sup>This work was supported by a Federal Health Grant.

hexosamine.

## 2. Hexosamine Values in Terms of the Mean .-

25 nonpregnant healthy women = 82.7 mg. % (S.D. = 4)	25	nonpregnant	healthy	women	=	82.7 m	9. %	(S.D.	=	4
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25 women at term 
$$= 104.5$$
 mg. %

19 cases of rheumatoid arthritis = 130 mg. %
Table II shows a comparison between the Rose-Waaler titers and serum

TABLE II. RELATIONSHIP BETWEEN ROSE-WAALER TITERS AND SERUM HEXOSAMINE CONTENT

			R	OSE-WAAI	ER TITERS			
	1/	16	1/3	32	1/6	14	1/128 ANI	ABOVE
	MINE (MG. %)	NO. OF CASES	HEXOSA- MINE (MG. %)	NO. OF CASES	HEXOSA- MINE (MG. %)	NO. OF CASES	HEXOSA- MINE (MG. %)	NO. OF
Abortion Rheumatoid arthritis	95	9	97 100	9	132 133	7	131	- 0

## 3. Seromucoid Values in Terms of the Mean .-

$$37$$
 cases of abortion =  $73.6$  mg. %

Table III shows a comparison between the Rose-Waaler titers and sero-mucoid.

TABLE III. RELATIONSHIP BETWEEN ROSE-WAALER TITERS AND THE SERUM SEROMUCOID CONTENT

			R	OSE-WAAI	LER TITERS			
	1/1	6	1/3	2	1/6	34	1/128 AN	D OVER
	SERO- MUCOID (MG. %)	NO. OF CASES	SERO- MUCOID (MG. %)	NO. OF CASES	SERO- MUCOID (MG. %)	NO. OF CASES	SERO- MUCOID (MG. %)	NO. OF
Abortion Rheumatoid	75	16	72	9	73	11	73	1
arthritis	_		65	4	85	12	86	9

#### Comment

In a recent review on the chemistry of the mucoproteins Stary<sup>3</sup> drew attention to the conditions which cause a rise of these substances in plasma. The list is wide and includes surgical intervention, infection, rheumatoid arthritis, diabetes mellitus, and pregnancy. It is evident that any evaluation of the results of the examination of sera for hexose and hexosamine from patients suffering from spontaneous abortion must be measured against the physiological increase which occurs in normal pregnancy.

For hexose the results seem to be fairly clear. Normal pregnancy at term shows an increase in concentration by approximately 20 mg. per cent, about five times the standard deviation. In spontaneous abortion the increase is in the order of 40 mg. per cent, or ten times the standard deviation. Further, a comparison between serum hexose concentrations in abortion and

rheumatoid arthritis when related to the Rose-Waaler titer show a reasonable parallel in the findings. Serum hexosamine, on the other hand, shows a physiological rise due to pregnancy with no enhancement that could be related to the effects of spontaneous abortion and certainly not paralleled by the concentration which occurs in rheumatoid arthritis. When the hexosamine is equated with the Rose-Waaler titers in both spontaneous abortion and rheumatoid arthritis, however, different results are obtained. It will be seen that at a Rose-Waaler titer of 1/64 both conditions show a similar concentration of hexosamine which is well above the normal level.

Serum seromucoid concentration does not appear to be affected by preg-There is little difference between the pregnancy and nonpregnancy In abortion the mean concentration is 12 mg. per cent above blood levels. normal, three and one-half times the standard deviation, and in rheumatoid arthritis it is still higher, being 20 mg. per cent above the normal concentration, or six times the standard deviation. A comparison between blood seromucoid content and the Rose-Waaler titers shows that the increase of seromucoid is not related to titer, being approximately the same concentration irrespective of the Rose-Waaler reaction. In this respect seromucoid and hexose are similar and differ from hexosamine in which the rise in titer and increase in serum hexosamine run parallel.

The curious relationship in disease pattern between spontaneous abortion and rheumatoid arthritis already adduced from histological and serological evidence finds further confirmation in biochemical similarity.

# Summary

Serum hexose, hexosamine, and seromucoid have been estimated in healthy nonpregnant women, women in the first trimester of pregnancy, women at term, in cases of spontaneous abortion at the time of abortion, and in cases of rheumatoid arthritis. At the same time the Rose-Waaler titer was measured in the last two conditions. Serum hexose and seromucoid show a distinct rise in blood concentration in spontaneous abortion and rheumatoid arthritis when compared to the controls; this increase does not appear to be related to the Rose-Waaler titer. On the other hand the results suggest a distinct linkage between hexosamine levels and the Rose-Waaler titer.

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# THE PROBLEM OF SPONTANEOUS ABORTION\*

VII. Prematurity and Spontaneous Abortion

J. D. Gray, M.D., Carl Tupper, M.D., and J. A. Rowse, Halifax, Nova Scotia

(From the Department of Pathology, Halifax Infirmary and the Department of Obstetrics and Gynecology, Dalhousie University)

THE possibility has been considered that premature birth in apparently healthy women might be related to the same factors which appear to be associated with spontaneous abortion.<sup>1, 2, 3</sup> If they share a similar mechanism then the maternal serum should show increased amounts of sensitized sheep cell agglutinating substance and the placental villi evidence of proliferative lesions. This hypothesis has been put to test and the results are presented.

### Methods and Materials

Serum was obtained (1) from the blood of women with normal pregnancies at the seventh month, (2) from women and from the cord blood of their babies after full-term delivery, and similarly, (3) from women who were delivered prematurely. The serum was titrated for sheep red cell agglutinating properties by the technique already described. The placental villi in the premature series were stained by methods previously reported. The first 2 groups were controls for the third. Prematurity was defined as delivery at least 2 or more weeks before term of a baby whose weight was 5 pounds or less. As far as could be determined the women in all three groups were in good general health.

#### Results

The control series agglutination titers are shown in Tables I and II. The values for the infant's cord blood are opposite those of the corresponding mother in Table II.

The maternal Rose-Waaler levels at 7 months' pregnancy and term are in keeping with those we have already reported for normals. In 8 of the 10 cord bloods, small amounts of sensitized sheep cell agglutinating substance were present suggesting that the villous epithelium presents no great barrier to its passage when related to the concentration found in the serum of normal woman.

Table III gives the results of a similar examination in 25 cases of premature birth with the parallel histological observations in the placental villi.

An analysis of the 25 cases shows that 22 have pathological titers, 7 of them, 1 in 128 and above. These titers are, on the whole, higher than those seen in spontaneous abortion. The cord blood titrations in this group also

<sup>\*</sup>This work was supported by a Federal Health Grant.

demonstrate an increased titer in comparison with the controls. This rise appears to be associated with the height of the maternal titer, for if a comparison is made between sufficient numbers in the two groups the value for the titers expressed as averages is as follows: 10 controls, maternal titer \( \frac{1}{8} \) and under—cord blood average 1 in 2.6; 9 prematures, maternal titer \( \frac{1}{128} \) and above —cord blood average 1 in 6.7; 7 prematures, maternal titer \( \frac{1}{128} \) and above —cord blood average 1 in 13.

TABLE I. ROSE-WAALER TITERS IN WOMEN AT THE SEVENTH TO EIGHTH MONTH OF NORMAL PREGNANCY

CASE NO.	CONTROL	TEST	ABSORPTION
1	1/2	1/4	1/2
2	1/2	1/2	1/2
3	1/4	1/8	1/2
4	1/2	1/8	1/2
5	1/2	1/8	1/4
6	1/2	1/8	1/4
7	1/2	1/4	1/2
8	1/2	1/4	1/2
9	1/2	1/8	1/2
10	1/2	1/2	1/2
11	1/2	1/4	1/4
12	1/2	1/2	1/2

TABLE II. ROSE-WAALER TITERS FROM WOMEN AND THEIR BABIES AT TERM

CASE		MATERNAL			FETAL	
NO.	CONTROL	TEST	ABSORBED	CONTROL	TEST	ABSORBED
1	1/2	1/4	1/2	1/0	1/4	0
2	1/2	1/8	1/4	0	1/1	1/2
3	1/2	1/8	1/4	0	1/1	0
4	1/4	1/8	1/4	0	0	0
5	1/4	1/6	1/4	0	1/0	0
6	1/4	1/8	1/4	0	0	0
7	1/4	1/8	1/6	1/2	1/4	1/9
8	1/4	1/8	1/4	0	1/2	0
9	1/4	1/8	1/4	0	1/4	1/2
10	1/2	1/1	1/6	0	1/2	0

There appears to be some limit to the amount of agglutinating factor the villous epithelium will admit, for irrespective of the height of the maternal titer the greatest found in cord blood was ½6.

Cold agglutinins were present in the maternal serum of 15 cases. They were not found in the cord blood. The cold antibodies were unusual in that the reaction occurred only in the control row while the sensitized and absorption rows remained unaltered. Some of the results are shown in Table IV. After abolition of the cold antibody effect by exposure of the test to 37° C. for an hour, reversal could be obtained by refrigerating the tubes at 4° C. for another hour. The cold agglutinin encountered is obviously nonspecific for it is active against sheep cells. It would appear that the inability of this agglutinin to act on the sensitized cells is due to the activity of the rabbit serum anti-sheep cell hemolysin, for in its presence cold agglutination is unable to take place, possibly because of blockage at the sheep red cell receptor sites.

Fig. 1.—A placental villus. Normal 3 months' pregnancy. (Hematoxylin and eosin.  $\times 180\,;$  reduced  $\frac{1}{2}.)$ 

Fig. 2.—Placental villi. A normal 7 months' pregnancy. (Hematoxylin and eosin. X180; reduced ½.)

Fig. 3.—Placental villi. A normal full-term pregnancy. (Masson's trichrome. ×180; reduced ½.)



Figs. 1-3. For legends see opposite page.

TABLE III. ROSE-WAALER TITERS IN MOTHERS AND BABIES AND THE PLACENTAL HISTOLOGICAL CHANGES IN 25 CASES OF PREMATURE LABOR

					TITERS	RS				
CASE		WEEKS		MATERNAL	.7		FETAL		VILLOUS	
NO.	PARA	PREMATURE	CONTROL	TEST	ABSORBED	CONTROL	TEST	ABSORBED	HISTOLOGY	REMARKS
1	Primipara	4	1/4	1/8	1/2	0	0	0	Normal	
67	Primipara.	61%	1/1	1/4	1/6		Insufficient		Normal	1
00	Para ii	316	1/2	160	1/2	0	1/6	0	Normal	
4	Para i	000	1/4	1/32	1/4	0	1/2	0	Proliferative	
4		)	*	/10	*/		*	)	to fibrinoid	
10	Para ii	10	1/2	1/01	1/8	0	1/4	1/6	Proliferative	
9	Para iii	0.00	1/2	1/99	1/0	0	1/4	0	Fibrinoid	2 Previous abortions
1	Para iv	9	1/2	1/44	1/2	1/2	1/2	1/3	Fibrinoid	3 Previous abortions
00	Para i	4	1/2	1400	1/0	0	1/16	0	Proliferative	1
6	Para iii	ବଳ	1/2	1,128	18	0	1/8	0	Proliferative	1 Premature, 1 abor-
										tion
10	Para v	4	1/4	1/64	1/8	1/2	1/8	1/4	Proliferative	1 Premature
11	Primipara	61	200	1/8	1/2		Insufficient		Proliferative	ı
12	Para xvi		1/2	1/99	1/4	0	1/8	1/2	Proliferative	2 Previous abortions
13	Para 0	63	1/4	1/16	1/4	0	1/4	70	Proliferative	2 Previous abortions
14	Primipara	-	1/4	1/198	1/18	0	1/16	1/2	Proliferative	1
15	Para iv		1/4	1/198	1/8	0	1/16	1/4	Juvenile	1
16	Para vi	6 (twins)	1/2	1,128	1/82	00	37	00	Normal	2 Previous prematures
17	Para ii	10	1/8	1/39	1/8	0	1/14	0	Fibrinoid	1 Previous abortion
18	Primipara	14	1/2	1/64	1/8	0	1/2	0	Fibrinoid	-
19	Primipara	41%	1/4	1/64	1/4	0	1/8	1/2	Proliferative	
20	Primipara		1/2	1/64	1/8/				Juvenile	I
21	Primipara.	6	1/2	1/190	1/89	0	1/10	0	Proliferative	
22	Para vii		1/2	1,256	1/82	0	1/10	1/2	Proliferative	1 Premature, 3 abor-
53	Para ii	ಣ	1/4	1/64	1/18	0	1/8	0	Proliferative	1 Abortion
24	Para 0	භ <del>4</del>	2,7	77	1/2	0	1/4	1/2	Proliferative Proliferative	Habitual aborter
00	I ala o	+	₹-/ <sub>2</sub>	716	/22				A LOUIS OF SECTION	ALCOLUMNA UNDOLONE

The histological changes present in the placental villi closely resemble those seen in spontaneous abortion. In no case, however, had the intravillous collagen proliferation destroyed the vascular tree completely, as is frequently seen in cases of abortion; nor were the ovoid plaques of fibrinoid necrosis common. The villous epithelium appeared normal.

TABLE IV. COLD AGGLUTININ EFFECT IN THE SERA OF MOTHERS OF PREMATURE INFANTS

		4 4° C.			37° c.	
CASE NO.	CONTROL	TEST	ABSORBED	CONTROL	TEST	ABSORBEI
1	1/16	1/84	1/8	1/1	1/04	1/8
2	1/32	1/256	1/22	1/2	1/256	1/32
3	1/16	1/128	1/16	1/4	1/128	1/16
4	1/8	1/32	1/2	1/2	1/32	1/2
5	1/8	1/64	1/8	1/2	1/64	1/8
6	1/16	1/04	1/16	1/4	1/64	1/16

Fig. 1 shows a villus from a normal pregnancy of about 3 months. Figs. 2 and 3 show villi from normal 7 month and term placentas. The stromal lacelike pattern is evident in all three and, to us, is the basic characteristic of normal. The histological changes in the villi between the end of the first trimester and the beginning of the last consist in a condensation of the epithelium to a syncytial layer, loss of Hofbauer cells, enlargement of the vessels and thickening of their walls, condensation and enlargement of the stromal fibers, and regression in the amount of ground substance. Between the beginning of the third trimester and the end of pregnancy the villous changes are not marked but there is a further increase in thickness of the vessel wall and the ground substance is now almost replaced by the stromal fibers.

The usual villous pattern seen in prematurity is that of stromal cell proliferation. Cell nuclei are large, round to ovoid, rather than spindle shaped. Between the cells collagen fibrils run erratically through the intravillous space destroying the regularity of the normal architecture. This proliferative exuberance is accompanied by a reduction in the number and diameter of the villous blood vessels. The intervillous spaces are usually empty. These lesions of prematurity show some patchy distribution throughout the placenta such as is seen in spontaneous abortion.

This proliferative reaction is illustrated in Figs. 4, 5, and 6. Fig. 4 is from Case 21 and shows a moderate degree of villous collagenization. In Fig. 5 from Case 11, collagen has so filled the villus that the vascular tree is nearly obliterated. Fig. 6 from Case 4 shows a plaque of fibrinoid necrosis.

In 8 of the cases (Nos. 4, 7, 14, 15, 17, 19, 20, and 23), there was a marked discrepancy in maturation of the villi. That is to say, regardless of the duration of the pregnancy the placenta showed villi of different ages. In some areas they resembled those seen at the fourth and fifth months of pregnancy and in others an architecture chronologically in keeping with the given time of conception. In many cases admixed with juvenile villi were those showing the gross collagenization already described.

Fig. 7 from Case 20 illustrates a juvenile villus. According to the patient's dates, she was within a month of term when delivery took place. If this picture is compared with Fig. 2, which shows a normal 7 month villus, the extraordinary discrepancy in age can be appreciated. Even an allowance of a month for mistiming on the patient's part will not narrow the breach between the "juvenile" and the normal. A closer approximation to the histological age of these villi appears when comparison is made with Fig. 1, a first trimester villus.

Fig. 7.

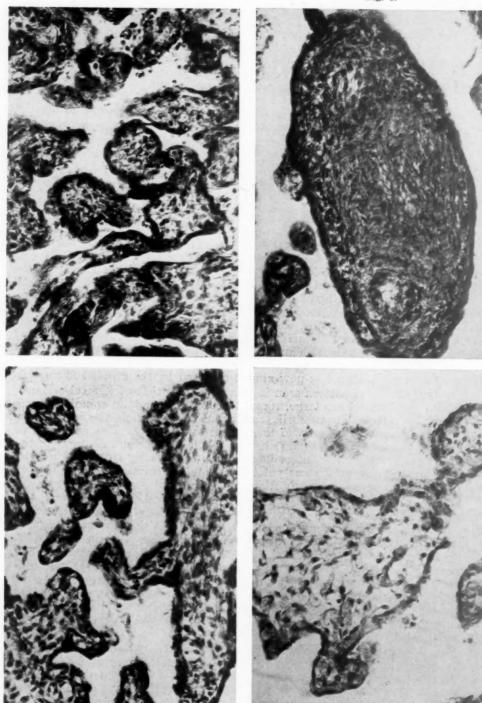


Fig. 6.

Figs. 4-7.—For legends see opposite page.

In 21 of the 25 cases of prematurity, pathological villi were seen in the placental examination; all had increased Rose-Waaler titers. Two cases had increased titers and normal placentas, one case a normal titer and a pathological placenta, and one, a normal titer and normal placenta.

It is interesting to note that if the 8 primiparas are removed from the group of 25 cases, 12 of the resulting 17 show a previous history of either prematurity or spontaneous abortion, an incidence of 70 per cent.

#### Comment

Peel4 divided the causes of prematurity into three groups:

- 1. Those in which maternal conditions might be held responsible, such as nephritis, chronic hypertension, diabetes, toxemia, etc.
- 2. Conditions occurring within the uterus, such as multiple pregnancy, hydramnios, and premature rupture of the membranes.
- 3. The so-called "idiopathic," under which heading about 50 per cent of the cases fall. He was careful to point out that in the first two groups prematurity may be coincidental and not caused by maternal or intrauterine conditions.

The conflict of opinions on the etiology of prematurity<sup>5</sup> suggests that none advanced so far adequately fit the frame of reference.

The evidence presented strongly suggests that spontaneous abortion and "idiopathic" prematurity arise from the same cause. The maternal sera in both show pathological Rose-Waaler titers and the placental villi exhibit similar lesions. If collagen disease is to be regarded as a condition which exhibits focal collagen proliferative changes in tissue and the presence of sheep cell agglutinating substance in the serum they both qualify for the title. The differences between them are those of degree. The villous lesions in prematurity never reach the intensity shown in abortion for in the latter complete vascular ablation often occurs, a state never seen in the former. In prematurity the ground substance may be diminished; in abortion it is often replaced by complete villous collagenization. Fibrinoid necroses appear occasionally in the premature villus but commonly in that of spontaneous abortion. The villous epithelium, as far as can be judged by the stains used, appears normal in prematurity; in abortion it is occasionally atrophic. Why some of the villi in prematurity should lag in maturation we do not know.

The Rose-Waaler titers reach higher levels in prematurity than in abortion, a difference that may be ascribed to life and death. In the first, the interaction between mother and fetus carries on until birth takes place; in the second, fetal death supervenes early, usually sometime before the abortion occurs. It seems reasonable to consider that the rapid decline in fetal cell metabolism that takes place in abortion should result in an equally precipitous fall of the stimulant responsible for the maternal production of sheep red cell agglutinating substance, or in immunological terms the maternal serum antibody concentration is a reflection of antigen output by the fetus.

Fig. 4.—Placental villi. Premature delivery. Early proliferative phase. There is marked reduction in the vascularity. (Hematoxylin and eosin.  $\times 180$ ; reduced  $\frac{1}{20}$ .)

Fig. 5.—Placental villi. Premature delivery. Generalized collagenoses. Blood vessels nearly obliterated. (Masson's trichrome. ×180; reduced ½.)

Fig. 6.—Placental villus. Premature delivery. Stage of fibrinoid necrosis. (Masson's trichrome, ×180; reduced ½,)

Fig. 7.—Placental villi. Premature delivery. "Juvenile" villi. (Hematoxylin and eosin. ×180; reduced ½.)

We would suggest that whether a case terminates in spontaneous abortion or in prematurity is governed by the speed and intensity of the reaction in the villi. Where both are marked, abortion results; where both are slow, prematurity follows.

The appearance of the cold agglutinin in this series is probably of little importance. Most of the investigations were done in the late fall and early winter, during and after the influenza epidemic, and the occurrence of this antibody is likely related to the presence of a virus.

# Summary

An inquiry into a possible relationship between spontaneous abortion and premature labor has been made.

It has been shown that in 21 of 25 cases of premature birth there were pathological lesions in the placental villi; in all these cases there was agglutinating substance in the maternal serum. Smaller amounts of this substance pass through the villous epithelium into the fetal circulation.

The histological and serological patterns in prematurity and spontaneous abortion are almost identical; the difference is one of degree only. It is suggested that this difference is responsible for the end result in any given case.

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# REPAIR OF INCOMPETENT CERVIX IN A CASE OF TWIN PREGNANCY\*

RICHARD FRANK, M.D., AND FRANK E. RUBOVITS, M.D., CHICAGO, ILL.

(From the Division of Obstetrics and Gynecology, Michael Reese Hospital)

THE syndrome of the incompetent cervix with its implications in midtrimester abortions was introduced into the literature by Lash and Lash<sup>3</sup> in 1950. Since that time several publications have confirmed the original concept, and the rationale of a repair of such a cervix has been widely accepted. Most such operations have been carried out on the nonpregnant uterus, although Shirodkar,<sup>5</sup> of Bombay, and more recently Baden,<sup>1</sup> from Texas, Parks and his group,<sup>2</sup> from Washington, and McDonald,<sup>6</sup> in the British literature, reported successful repairs of the yielding incompetent cervix during pregnancy. All reports agree that ruptured membranes constitute a contraindication to a repair.

## Case Report

Mrs. S. G., age 33, married, gravida ii, para i, was first seen on Oct. 3, 1957. The past history was noncontributory with the exception that the previous pregnancy was carried to full term, but that delivery after prolonged labor was accomplished by difficult "high forceps." The present pregnancy had been uneventful up to the time of the first visit, when the expected date of confinement was thought to be Jan. 3, 1958. The patient had arrived from overseas 2 days earlier and presented herself with the complaint of losing amniotic fluid for the past few hours.

There were no uterine contractions present. Abdominal examination revealed a fundus at a height of 28 to 30 weeks' gestation; fetal heart tones were present; fetal parts could not be made out with certainty. Vaginal examination revealed a parous outlet with marked varicosities of the vulva and a redundant vaginal mucosa. The cervix was patulous and an irregular structure was felt in the cervical canal. The cervix could be exposed only with the patient in the knee-chest position, and toes and part of a foot were visualized in the cervical canal. The patient was hospitalized immediately. X-ray examination of the abdomen revealed a twin pregnancy of about 26 weeks, corresponding with the menstrual data. The patient was placed on antibiotics. When no labor had ensued 24 hours later, it was decided to attempt surgical closure of the incompetent cervix.

Under spinal anesthesia, a weighted retractor was inserted into the vagina. At this time a fetal leg and approximately 10 inches of pulsating cord had prolapsed through the cervix into the vagina. With two ring forceps on the cervix, the prolapsed leg and cord were gently replaced into the uterus and kept there by inserting a moist sponge through the long patulous cervix. A strip of ox fascia lata was placed in purse-string fashion around the cervix, approximately one inch above the external os. This was accomplished

<sup>\*</sup>Presented before the Chicago Gynecological Society, April 18, 1958.

with one finger in the cervical canal to ascertain that the entire thickness of the cervix proper was included in each bite of the suture which was threaded on a heavy full-curved hernia-repair needle. During this procedure an old sulcus tear on the right side, arising from the external os and going past the internal os of the cervix, was visualized. The completed purse-string suture was firmly tied, resulting in closure of the internal os. No bleeding ensued. Reinforcing mattress sutures of heavy black silk were placed anteroposteriorly through the cervix below the purse-string suture.

The postoperative course was uneventful. The patient was kept at bed rest and on antibiotics. Cervical cultures remained sterile. After 10 days antibiotics were discontinued, and the patient continued an afebrile course without uterine contractions until 18 days following the operative procedure, when the temperature rose to 99.6° F. The patient complained of vague backaches. No contractions were noted, but examination of the vulvar pad one hour later revealed that the labia were slightly distended by the presence of two fetal feet. One half hour later a stillborn female infant was delivered spontaneously with manual aid. The infant was not macerated and the estimated weight was 2 pounds. This delivery was accomplished without any palpable or subjectively noticeable uterine contractions.

After 45 minutes had elapsed without uterine contractions an intravenous infusion with Pitocin was started, but the resulting contractions were few and far between. Thirty minutes later, the bulging bag of waters was ruptured and a compound presentation was encountered in the inlet. Fetal heart tones were not obtainable either prior to or after rupture of the membranes. A podalic version was attempted, but could not be carried out with ease. Therefore, a combined internal and external cephalic version was performed, and, with speeding-up of the Pitocin infusion, uterine contractions resulted which accomplished the descent of the fetal head, and 20 minutes later a male infant was delivered spontaneously. The baby breathed spontaneously and was immediately placed in oxygen. The placenta and membranes were delivered spontaneously 20 minutes later.

The postpartum course was uneventful. The surviving baby weighed 2 pounds, 6 ounces, at birth, and at this writing weighs over 14 pounds and is doing well. Postpartum visualization of the cervix showed the purse string of fascia lata to be torn but partially still present in the cervical tissues.

#### Summary

This is a case report of a patient with twin pregnancy, in whom a leg and a loop of cord had prolapsed through an incompetent cervix after spontaneous rupture of the membranes at 26 weeks. Replacing the fetal parts and closing the cervix surgically prolonged the pregnancy for 18 days.

In general, ruptured membranes are a contraindication to this surgical procedure. The repair nevertheless was undertaken because the twin pregnancy presented one ruptured bag of waters and an intact one on the second twin.

The above-described procedure was carried out with relatively happy results. One infant is surviving and doing well. No infection of the mother occurred.

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# MATERNAL DEATH FOLLOWING SUTURE OF INCOMPETENT CERVIX DURING PREGNANCY

Leo J. Dunn, M.D., J. Courtland Robinson, M.D., and Charles M. Steer, M.D., New York, N. Y.

(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia Presbyterian Medical Center and the Sloane Hospital for Women)

WITHIN the past decade increasing attention has been directed toward a new syndrome, that of late abortion due to the incompetent cervix. Since the first descriptions by Lash¹ in this country and Palmer² in France, a large number of cases have been discovered. Little is known regarding the frequency of this condition. Baden and Baden³ have estimated the occurrence to be one in 300 consecutive pregnancies. The exact nature of the anatomical defect is as yet undecided. Some authors consider the internal os as primarily responsible; others feel that the entire cervix is at fault. The defect may be purely an anatomical one, although neuromuscular and endocrine factors have been suggested.

The repair of the cervix in the nonpregnant state is well known and has become a standard procedure, but more recent have been the diagnosis and repair during pregnancy. Since the first published paper by Shirodkar,<sup>4</sup> many cases have been surgically treated by a variety of techniques. A brief review of the literature to date discloses report or mention of 137 surgically treated patients.<sup>4-7</sup> In these cases there has been an over-all success rate of approximately 61 per cent. The morbidity of these procedures apparently has been negligible since only minor bleeding episodes or inconsequential infections have been briefly mentioned. Death has not been previously reported as a complication.

This is the report of a maternal death following the surgical repair of an incompetent cervix during pregnancy.

A 26-year-old white gravida ii, para 0, whose last menstrual period was May 25, 1957, was admitted on Nov. 11, 1957, with the complaint of painless vaginal bleeding. The patient had had two previous admissions to Sloane Hospital. During her first pregnancy in 1953 she was admitted with premature rupture of the fetal membranes and vaginal bleeding. Examination revealed an inevitable abortion of a pregnancy of approximately 14 weeks' gestation. The patient was treated with Pitocin followed by a dilatation and curettage. No abnormalities of the uterus were noted. The second admission in 1956 was for premenstrual dysmenorrhea and metrorrhagia. At dilatation and curettage no abnormalities were noted and the curettings showed inadequate secretory endometrium.

In this pregnancy, the last menstrual period was on May 25, 1957. She was first seen in the Sloane Ante-Partum Clinic on Aug. 9, 1957. Physical examination was normal except for enlargement of the uterus, which was, however, smaller than expected by about 4 weeks' development. A 24 hour pregnancy test on Aug. 12, 1957, was negative. The patient was then followed in the clinic where repeated examinations indicated that the uterus was enlarging, and a repeat pregnancy test on Oct. 4, 1957, was positive. The case was then followed in the clinic as a normal intrauterine pregnancy until the day of admission. On the day of admission the patient noted painless vaginal bleeding without contractions. No clear fluid was passed per vaginam.

Physical examination on admission showed blood pressure 120/80, pulse 84, and temperature 98.8° F. The fundus was palpated to the umbilicus, and the fetal heartbeat was audible in the left lower quadrant and regular. Rectal and pelvic examinations The remainder of the examination was within normal limits and the patient was admitted as having a threatened late abortion. Laboratory studies at that time were as follows: hemoglobin 11.5 Gm., erythrocyte count 3.86 million, leukocyte count 11,800, neutrophils 83, hematocrit 37.4 per cent. The patient was placed on bed rest and sedation for 3 days during which time the vaginal bleeding stopped. Full ambulation was allowed with no return of bleeding. On the fourth hospital day pelvic examination disclosed a patulous cervix with the membranes protruding. No internal os was palpable. With these findings and a history of previous late abortion it was felt that the patient had an incompetent cervix. On Nov. 17, 1957, she was given 0.3 mg. of atropine with 30 mg. of Demerol intravenously and was taken to the operating room. Examination under Pentothal and nitrous oxide-oxygen anesthesia showed the complete absence of any internal os. A running suture of No. 0 braided silk was started on the posterior lip to include almost the full thickness of the cervix but not penetrate the mucosa. This was then continued around in a circumferential manner with small bites being taken in the more superficial portions of the cervix. The suture was placed in a concentric manner approximately 1.5 cm. above the external os. The membranes were reduced with gentle pressure by a small sponge on a stick and the suture was tied. Bleeding was negligible and the patient was returned to the ward on bed rest in Trendelenburg position. She was given hydroxyprogesterone caproate, 125 mg. intramuscularly daily, Luminal sodium, 90 mg. every 4 hours, Demerol, 50 mg. every 4 hours, and oral tetracycline, 250 mg. four times a day. On the third postoperative day the fetal membranes ruptured spontaneously. There were no contractions and the fetal heartbeat remained audible. Thereafter slight leakage of clear amniotic fluid continued but fetal activity remained normal and there were no contractions. No pelvic or rectal examinations were performed. The temperature remained normal. On the eighth postoperative day the patient experienced a sudden shaking chill and her temperature rose rapidly to 106° F. She became completely disoriented and belligerent. Blood for culture was drawn immediately. Pelvic examination showed the cervical suture to be lying free in the vagina. The cervix was 2½ fingers dilated and showed no evidence of inflammation save at the suture sites. The amniotic fluid was slightly cloudy but not foul smelling. The fetal head protruded into the lower uterine segment. The uterus extended to the umbilicus and was soft and nontender. No contractions were noted. The remainder of the physical examination was negative. There was no costovertebral tenderness and the lungs were clear. The temperature continued to rise and within minutes reached 107.2° F. per rectum. Therapy was instituted with oral aspirin, alcohol sponges, and an infusion of 1,000 c.c. 5 per cent dextrose in water containing 10 million units of penicillin and 1 Gm. of chloramphenicol. The total 24 hour dosage of antibiotics was 41.2 million units of penicillin, 4 Gm. of chloramphenicol, and 1 Gm. of streptomycin. During the acute onset of the illness the patient's blood pressure decreased from the previous level of 120/80 to 80/40 and remained at this new level. A complete blood count included a hemoglobin of 9.8 Gm., a leukocyte count of 8,150 with 92 per cent neutrophils and a marked shift to the left. The impression at this time was that she had an intrauterine infection with no evidence of parametritis. Accordingly, intramuscular Pitocin, 5 units every 30 minutes, was administered and after 90 minutes the patient passed an 800 gram fetus and an apparently intact placenta. The fetus and placenta were foul smelling. Cultures were taken of the uterine cavity and placenta. The fetus was dead but showed no evidence of maceration.

Following delivery the temperature remained at 101°-100° F, the blood pressure at 70/30, and the urinary output was 50 c.c. per hour. Medical consultation was obtained and the clinical diagnosis of overwhelming sepsis was confirmed. The antibiotic coverage was deemed appropriate and the blood pressure level was considered adequate in view of the satisfactory urinary output. Nasal oxygen was started 12 hours after onset because of the complaint of slight dyspnea although examination of the lungs continued to be negative. Four hours later the blood pressure suddenly became unobtainable. Intravenous ephedrine was administered with prompt pressor response and a continuous norepinephrine drip was started with 8 mg. of bitartrate per 1,000 c.c. 5 per cent dextrose in water. Three hours later the patient developed pulmonary edema. This episode responded to rotating tourniquets and positive pressure oxygen. Intravenous digitalization was instituted with Cedilanid, 1.2 mg., followed in one hour by 0.4 mg. Pulmonary edema recurred twice and each time responded readily to the previous regimen. The patient required progressively increasing concentrations of norepinephrine to maintain the blood pressure above 70/30. Urinary output continued at approximately 55 c.c. per hour. An electrocardiogram showed myocardial disease and drug effect and a chest x-ray indicated cardiomegaly with scattered radiodensities consistent with pulmonary edema. In spite of all measures, the patient's clinical condition continued to deteriorate with the development of peripheral and central cyanosis. A gallop rhythm developed and the heart sounds were of poor quality. Twenty-nine hours after the onset of the illness the patient died.

Cultures of blood, placenta, uterine cavity, and fetal lung grew out *Escherichia coli* sensitive to chloramphenicol, polymixin B, Furadantin, and streptomycin, and resistant to tetracycline.

A complete postmortem examination was performed 22 hours after the patient's demise. Cyanosis of the nail beds, lips, and all mucous membranes was noted. The abdominal cavity was free of fluid and the uterus extended 4 cm. above the symphysis pubis. The surface of the uterus was smooth, glistening, and congested. The uterine wall was 1.5 cm. in depth, flabby, and of pinker color than usual. The endometrial surface was dull and shaggy in appearance with gray and red mottling. On the posterior-superior surface of the cavity there was a 5 cm. patch of blood clot mixed with necrotic friable debris. The cervix was soft and congested both on the external surface and on sectioning. There were three minute breaks in the cervical mucosa in the portio vaginalis. The vagina was congested with an abundant layer of creamy exudate in the upper vagina covering the portio vaginalis. The parametria showed mild congestion. The ovaries and Fallopian tubes were congested. The ovaries measured 6 by 4 by 1.5 cm. The bladder mucosa was congested throughout with three 1 cm. foci of intramucosal hemorrhage.

The kidneys together weighed 360 grams and were joined at the lower poles in a "horseshoe" malformation with separate pelves and ureters. The parenchyma was congested and the upper medulla dark red. The ureters were normal. The adrenal glands were normal with a 2 mm. cortex. The liver weighed 2,400 grams. The spleen weighed 200 grams, being soft and hemorrhagic, with no identifiable Malpighian bodies.

Each pleural cavity contained 500 c.c. and the pericardial sac 25 c.c. of clear serous fluid. The pleural surfaces were smooth and glistening. The heart weighed 300 grams and was moderately dilated with a globular shape. The epicardial and endocardial surfaces were smooth and glistening. The trabeculae carneae and columnae carneae were flattened. The myocardium was pale and flabby with 0.5 cm. hemorrhages in the papillary muscles and subendocardium of the left ventricle. The coronary arteries were normal.

The right lung weighed 700 grams and the left 600 grams. The pulmonary parenchyma was hemorrhagic throughout with marked loss of air crepitus especially in the lower lobes which sank in water. The bronchi were congested and filled with a foamy white liquid. The pulmonary vessels were normal. The gastrointestinal, central nervous, and musculoskeletal systems were essentially normal.

On microscopic examination extensive focal, acute, inflammatory changes were noted in the myocardium of the anterior papillary muscle of the left ventricle. Large numbers

of neutrophils, and edema, congestion, and hemorrhage were noted with extensive coagulation necrosis. The blood vessels contained many neutrophils but no colonies of bacteria were observed. The lungs showed diffuse edema and congestion with a high protein content exudate in the air spaces. The blood vessels contained many neutrophils with some perivascular infiltration. There was marked atrophy of the Malpighian follicles in the spleen with marked edema and numerous neutrophils. The adrenal glands were normal. In the kidneys there was extreme edema and congestion with extensive focal hemorrhage. There were focal streaky infiltrations of lymphocytes and disruption and distortion of many tubules throughout. The surface epithelium and stroma of the bladder were diffusely infiltrated by neutrophils and fibrin, with extensive recent hemorrhage in the affected areas. The blood vessels were distended with red cells and neutrophils.

In the uterus the placenta and decidua were infiltrated with numerous neutrophils. The myometrium showed hypertrophy of the muscle tissue with widespread dilatation of myometrial blood vessels which were filled with neutrophils. In the cervix there were subepithelial infiltrations of lymphocytes and plasma cells. Several small epithelial veins in the cervix showed endothelized thrombi plugging the lumina. The ovaries, parametria, and tubes all showed congestion with numerous neutrophils in the blood vessels. The bone marrow showed marked hyperplasia of the myeloid cells. The small intestine was normal with no evidence of pseudomembrane on the mucosal surface.

The cause of death was E. coli septicemia with acute necrotizing myocarditis.

#### Comment

This case is the first in which death has occurred following operation upon the dilated cervix during pregnancy. Death was due to an overwhelming infection with a strain of *E. coli* which was resistant to the antibiotic (tetracycline) which was being used prophylactically. This organism also happened to be one of an extremely virulent group which cause severe shock of the type seen in the Waterhouse-Friderichsen syndrome. The clinical course of this patient after the onset of her illness is remarkably similar to the cases of "placental bacteremia" described by Studdifords in septic abortions. There is also a basic similarity in the primary etiology of these cases, i.e., instrumentation of the pregnant uterus. This patient was treated prophylactically according to the usually accepted methods, but infection nevertheless supervened.

There are now reported some 137 cases in which this operation has been performed without death or any serious infection. Discussions with those interested in this problem from various parts of the world indicate that the total number of such operations actually performed, but not reported in the literature, may well be 1,000. It seems, therefore, that the true risk of infection with this operation is statistically quite small. The case described in this report seems to represent a most unfortunate combination of characters in the organism: resistance to the antibiotic and great virulence. This combination must be rare, but it will probably occur again sooner or later.

The value of the operation appears to be established; certainly there are a number of babies alive today who would have succumbed to extreme prematurity had the operation not been performed. This case raises the question as to whether the operation is worth the risk. The weight of numbers seems to answer this question in the affirmative. The operation cannot be considered without risk, but the risk is so small that it may be taken in many cases. The alternative would be to repair the cervix in the nonpregnant state. Whether this is actually safer, from the standpoint of infection, cannot be determined at this time. An organism of the type seen here could just as well produce infection in the nonpregnant state.

The prophylactic management of these cases has, in general, been similar to the management of this case. The choice of antibiotic has been made on the basis of (1) a wide spectrum of activity and (2) the smallest number of side effects, since the antibiotic will have to be given for a long time in some There are organisms which are resistant to every antibiotic, so that no theoretically perfect antibiotic can be chosen. Repeated cultures of the cervix would probably not show the virulent organism in cases such as these (where the organism grows in the placenta until it bursts into the blood stream) until clinical signs of infection have appeared. Conversely, the normal flora of the vagina and cervix would overgrow most cultures and give a sense of false security.

# Summary

This case is due to a rare combination of bacterial characteristics. The fact that a fairly large number of operations for the closure of the dilated cervix during pregnancy have been performed without a fatal outcome up to this case demonstrates that the likelihood of recurrence of this type of infection is quite small. The operation should probably therefore continue to be performed in properly selected cases, and the postoperative management of these cases should not be changed.

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## ADVANCED ECTOPIC PREGNANCY

JOHN F. J. CLARK, M.D., AND JOSEPH BOURKE, M.D., WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, Howard University School of Medicine and Freedmen's Hospital)

A DVANCED ectopic pregnancy is defined in this study as any gestation which develops outside of the endometrial cavity with a gestational age of 12 weeks or more. This definition differs, however, from that of some authors. Yahia¹ defines advanced ectopic pregnancy in his paper as any extrauterine gestation of an age of 5 months or more. King² uses near the period of viability. We feel that after the third month, and the formation of the placenta with all of its associated complications and its greater difficulty of management and hemorrhage, such gestations should be considered as advanced ectopic pregnancy.

#### Incidence

This is a study of advanced ectopic pregnancies from 1948 through 1957. During this 10 year period, 30 cases fell into this category. These 30 pregnancies were divided into 11 tubal, 17 abdominal, and 2 intraligamentous pregnancies. The ratio of ectopic pregnancy in our hospital is 1 to 84 pregnancies. This incidence of abdominal pregnancy is 1 in 1,746 pregnancies. The comparison of advanced ectopic pregnancy to the total group of ectopic pregnancies is 1 to 11.7.

Ectopic gestation is a frequent entity at our hospital. From the figures above it is evident that one ectopic out of every 11.7 goes past the twelfth week. The incidence is so high that ectopic gestation is always kept in mind when a woman in the childbearing period has an irregular menstrual period and abdominal pains. The abdominal pregnancy incidence quoted by Beacham³ was 1 in 2,081 pregnancies, with an incidence of tubal ectopic pregnancy of 1 in 106 pregnancies. Eastman⁴ states the figure for abdominal pregnancy as 1 in 15,000 deliveries.

### Procedure

The 17 abdominal pregnancies were divided into three groups as indicated in Table I. In Group A the placentas were located posteriorly to the uterus or in the cul-de-sac. In Group B they were not located on the posterior broad ligament or in the cul-de-sac. (They were usually located on the uterine fundus or the superior aspect of the Fallopian tube.) Group C includes secondary abdominal pregnancies that developed following early perforation or rupture of the uterus.

Group A.—In this group the placenta was usually located on the posterior leaf of the broad ligament or in the cul-de-sac (Fig. 1). These usually followed tubal abortions or implantation of the placentas on the fimbriated end of the

tubes. By x-ray or at laparotomy, the fetal back was located posteriorly. The fetal appendages were usually pointing toward the placenta. These cases were easier to diagnose and a separate mass from the uterus was palpated. The uterus was displaced upward under the symphysis, high on the large extrauterine mass. The cervices were usually firm. Symptoms were mainly from pressure or intraperitoneal bleeding. There were less abdominal symptoms such as nausea, vomiting, or awareness of fetal movements than in Group B. The fetuses were not very easily palpable. The gestations in this group ranged from 12 weeks to 39 weeks. The handling of placentas in these cases was not difficult because they were located on the posterior surface of the broad ligament, the tubes, and ovaries. These structures could easily be removed surgically.

ILLUSTRATIVE CASE: D. Q. (Case 8, Table I), a 27-year-old gravida iii, para i, woman, whose last normal menstrual period was Nov. 1, 1955, and whose estimated date of confinement was July 8, 1956, was admitted on July 31, 1956, because of vaginal spotting on July 2 and the discovery of a transverse lie on the date of admission (Figs. 4 and 5). She complained of upper right quadrant pain 2 days prior to hospitalization. Abdominal pregnancy was suspected and a pelvic mass separate from the fetus was palpated bimanually. Roentgenograms of the abdomen revealed a transverse lie with a portion of the fetal cranium

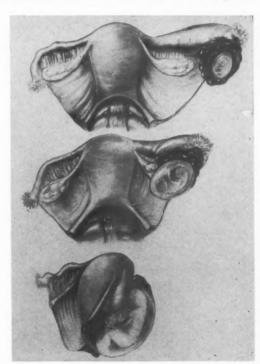


Fig. 1.—Development of abdominal pregnancy as in Group A.

posterior to the anterior aspect of the mother's spine on the lateral films. At laparotomy, a 39 week male fetus weighing 6 pounds, 3 ounces, was delivered alive. The placenta was attached to the posterior surfaces of the right broad ligament and tube. This was easily removed surgically. Convalescence was uneventful.

Group B.—The placentas were usually located on the uterine fundus or on the superior portion of the tubes (Fig. 2). One placenta was located on

the mesentery of the small intestine. This group, in general, was harder to diagnose. The pathogenesis of these cases was usually from a ruptured interstitial or isthmic tubal pregnancy. These gestations varied from 12 weeks

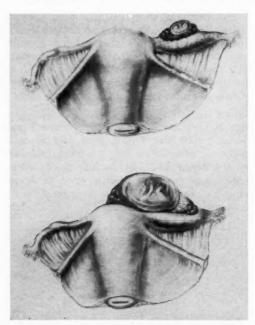


Fig. 2.—Development of abdominal pregnancy as in Group B.

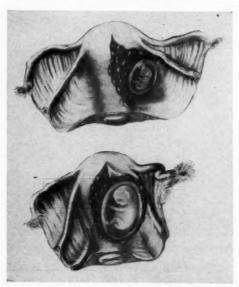


Fig. 3.—Development of abdominal pregnancy as in Group C.

to 38 weeks. The uterus in these pregnancies was usually pressed downward, located posteriorly, and not easily palpated. This would often give the false impression of a positive Hegar's sign of intrauterine pregnancy.

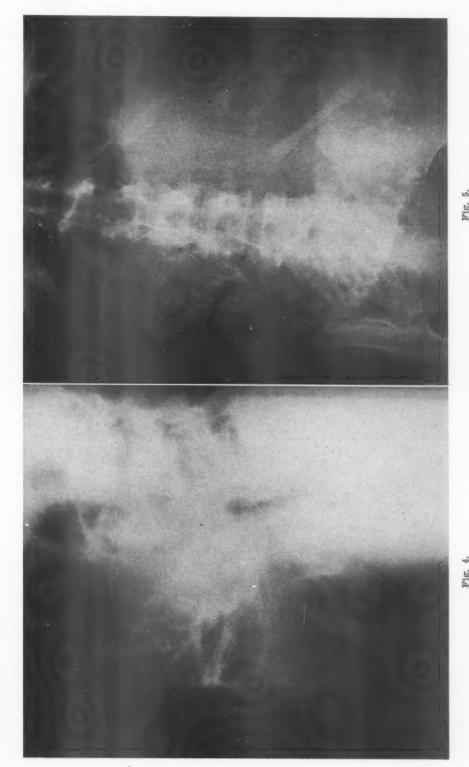


Fig. 4.—Lateral x-ray film demonstrating a fetus extrauterine with portion of the fetal cranium posterior to the anterior aspect of the mother's spine.

Fig. 5.—Typical x-ray findings in advanced abdominal pregnancy as described in illustrative case (Case 8).

TAB E	1
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CASE NO. AND INITIALS	GROUP	AGE	GRA- VIDITY	PARITY	CHIEF COMPLAINT	TYPE	GESTATIO : LENGTH (WEEKS
Abdominal	Pregnan	icu.—		1		1 222	(WEEKS
1. A. J.	A		i	0	Pain in L.L.Q.	Abdominal secondary to tubal abortion	16
2. J.G.	A	33	i	0	Pain in L.L.Q.	Abdominal secondary to tubal abortion	16
3. V. W.	A	34	ii	i	Epigastric pain, gas pains	Abdominal secondary to tubal abortion	* 28
4. E. T.	A	33	iii	ii	Pain in R.L.Q. for one month	Abdominal secondary to tubal abortion	12
5. M. H.	A	25	ii	i	Pain, fainting	Abdominal secondary to rt. tubal abortion	12
6. E.R.	A	31	i	0	Abdominal cramps	Abdominal secondary to ruptured lt. tube	20
7. E.B.	A	42	iii	ii	Bleeding	Tubo-abdominal	12
8. D. Q.	A	27	iii	· i	Vaginal spotting	Abdominal secondary to tubal abortion	39
9. C. W.	В	35	ii	i	Dead fetus	Abdominal secondary to tubal abortion	38
10. C. G.	В	24	iii	ii	Pain in L.R.Q.	Abdominal (infected) secondary to tubal rupture	12
11. J. M.	В	37	ii	i	Epigastric pain	Abdominal secondary to lt. tubal rupture	25
12. P. N.	В	34	îi	i	Fetal death Transverse lie	Abdominal secondary to lt. tubal rupture	37

LOCATION OF

PLACENTA

I imbriated end of

ment, cul-de-sac

tube, and ovary,

sigmoid, rectum,

and cul-de-sac

broad ligament, lt.

Fost. aspect lt.

FATE

OF PLA-

POSTOPERA-

TIVE DIAG-

TWO

MASSES

PALPATED

Yes

Yes

TAB E

'ATIO VGTH EKS

16 6

8

Interior surface uterine fundus. over lt, tube and

posterior surface

of bladder

DIAGNOSIS NOSIS Left tubo-ab-Left tubal lt. tube, broad ligapregnancy dominal pregnancy Same

Same

abdominal

pregnancy

Abdominal pregnancy Abdominal

PREOPERATIVE

Post, surface of uterus, rt. tube pregnancy and ovary, post. leaf of rt. broad ligament

Right tubo-Fimbriated end of Right tubal rt. tube, rt. ovary pregnancy and broad ligament, cul-de-sac

Rt. tube and broad Right tubal ligament, lateral pregnancy with hematowall of sigmoid cele Same

Posterior surface of Abdominal uterus, cul-de-sac, fimbriated end of pregnancy lt. tube and lt. ovary

Fimbriated end of Left ovarian Tubo-abdomcvst and inal preglt. tube, omentum, cul-de-sac uterine nancy fibroids Same

Abdominal Posterior surface rt. broad ligament, rt. pregnancy Anteriorly (sep-Abdominal

arated early) pregnancy

Infected ab-Interior wall of Infected ruputerus and over tured tubal rt. tube pregnancy Iesentery of small Abdominal Same

intestine, sigmoid, pregnancy caecum, post. sur-face of uterus (ruptured)

Placenta Abdominal previa pregnancy

Same

dominal

pregnancy

Left in

situ

CENTA SYMPTOMS OF UTERUS Removed Pain in L.L.Q. Anterior

CHIEF

Removed Persistent L.L.Q. pain, syncope, spotting

Removed Gas pains, Anterior constant epigastric pain, syncope, fetal movement

Removed R.L.Q. pain, slight bleeding for one month, ad-mitted in shock

Removed Pain, fainting, Anterior Abdominal pregnancy (cul-de-sac) rt. shoulder pain, shift-ing dullness

Removed Abdominal Anterior cramps, spotting, admitted in shock

Removed Bleeding

Removed Vaginal spot-Displaced to ting, transleft side verse lie Posterior Removed Signs of pre-

Anterior

Posterior

eclampsia (abated after cessation of fetal movement) Removed Pain, passage

of decidual cast Anterior **E**pigastric mass, syncope, con-

stant nausea and vomiting, fetal movement

Removed Nausea, vomit- Posterior ing, transverse lie, very active child

Anterior Yes

POSITION

Anterior and Yes anteplexed

Yes

Yes

Yes

Yes

No

No (not well de-

fined) Yes

No

TABLE I - CO. T'D

Anterior

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Anterior

Anterior

uterus

Posterio

Betwee rt. b

Betwee lt. b

CASE NO. AND INITIALS		GROUP	AGE	GRA- VIDITY	PARITY	CHIEF COMPLAINT	TYPE	GESTATION LENGTH (WEEKS)	
13.	E. G.	В	25	ii	i	Nausea, vomiting, upper abdominal cramps	Abdominal secondary to rupture rt. interstitial pregnancy	18	
14.	M. S.	В	34	iii	i	Labor pains	Abdominal secondary to rupture old cornual resection	32	
15.	8. W.	C	25	i	0	Dead fetus	Abdominal secondary to criminal perforation of uterus	- 20	
16.	E. F.	C .	27	iv	ii	Labor pains and bleeding	Abdominal secondary to rupture old classical scar	40	
17.	M. S.	С	34	iii	i	Fetal death	Abdominal secondary to occult rupture of interstitial pregnancy	24	
tral	igame	ntous P	regnar	ncy.—					
1.	I.S.		39	iv	iii	Pain in right side	Rt. intraligamentous	28	
2.	S. B.		40	i	0	Pain in L.L.Q.	Lt. intraligamentous	13	

ILLUSTRATIVE CASE: A 37-year-old gravida i, para 0, woman (Case 11, Table I), whose last normal menstrual period was Aug. 16, 1950, followed by 24 weeks of amenorrhea, was admitted to the hospital on Feb. 8, 1951, with a chief complaint of severe boring pains beginning in the epigastrium and radiating over the entire abdomen. Other complaints were syncope, persistent nausea and vomiting, and awareness of excessive fetal movement. The patient had had a myomectomy and an appendectomy in 1944.

A fetus the size of a 6 months' gestation was palpable abdominally and a uterus the size of a 3 months' gestation was palpable separately from the fetus on bimanual examination. General appearance, blood pressure, pulse, and the hematology were consistent with intraperitoneal hemorrhage, and a flat plate x-ray film of the abdomen revealed a 6 months' fetus. Preoperative impression was abdominal pregnancy secondary to a ruptured myomectomy scar. At laparatomy, the fetus was found to be enclosed in a sac encircled by transverse colon, small intestine, superior portion of the uterus, and mesentery of the small bowel. The myomectomy scar was intact, rupture having occurred from the left Fallopian tube. The placenta was attached to the uterus, mesentery of the small bowel, and a portion of the ileum. Surgically, the chief problem was to control bleeding from the separated free edges of the placenta without damaging the intestinal tract. This was done by the use of mattress sutures followed by packing with a 5 yard gauze roll, the placenta being left in situ. The pack was removed gradually over a period of 72 hours. The patient was discharged on the nineteenth postoperative day. As long as 9 months postoperatively some placenta could be palpated. Two years later, the patient had a contralateral tubal pregnancy. At that time, remnants of the old placenta were still found.

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LOCATION OF PLACENTA	PREOPERATIVE DIAGNOSIS	POSTOPERA- TIVE DIAG- NOSIS	FATE OF PLA- CENTA	CHIEF SYMPTOMS	POSITION OF UTERUS	TWO MASSES PALPATED
An erior surface uterus near junc- t on rt. tube and cornu, omentum	Abdominal pregnancy	Same	Removed	Pain in mid- line, nausea and vomit- ing, abdom- inal cramps	Posterior	Yes
Lt. side of uterus in pseudo sac com- nunicating with end. cavity	Fetal death in utero (infected)	Uteroabdom- inal preg- nancy	Removed	Fetal death in utero	Not palpated	No
Anterior surface of fundus, around old perforation	Ectopic cyesis (abd.) D.D.: Ovar. cyst, uterine preg.	Abdominal preg. (due to perforation)	Removed	Pain syncope	Displaced downward	Yes
Anterior surface of uterus along old scar	Abdominal pregnancy	Same (from old uterine disruption)	Removed	Constant nau- sea and vom- iting, fetal movement quite ap- parent	Posterior	Yes
Posterior surface of uterus	Fetal death in utero	Abdominal pregnancy (secondary)	Removed	Absence of fetal move- ment, trans- verse lie	Anterior (not palpated)	No
Between leaves of rt. broad ligament	Fetal death in utero	Right intra- ligamentous pregnancy	Removed	Pain in right side, absence of fetal movement for 3 months	Displaced to left side	No
Between leaves of lt, broad ligament	Ruptured left tubal preg- nancy	Left intra- ligamentous pregnancy	Removed	L.L.Q. pain, spotting, pelvic mass on left side	Displaced to right side	Yes

Group C.—This was a very interesting group because of pathogenesis. This group was due either to criminal perforations or to rupture of the uterus following previous surgery (Fig. 3). The first case listed (Case 15, Table I) was from a uterus perforated by attempted criminal abortion where the fetus and chorionic tissue continued to grow through an artificially made fistulous tract to the peritoneal cavity. The second case listed (Case 16, Table I) was due to a disruption of an old classical cesarean scar. The third patient (Case 17, Table I) had a partial salpingectomy in 1952 for right ectopic pregnancy. This time the pregnancy was implanted in the right cornual area and continued to grow after the remaining interstitial portion of the tube ruptured. Symptoms were similar to those in Group B.

#### Comment

We agree with Cross<sup>5</sup> that findings, such as palpation of superficial fetal parts, unusually loud fetal heart tones, inability to palpate the round ligament, Braxton Hicks contractions, false labor, or proof that the uterus was empty, were of little value to us. We found such things as persistent abdominal pains and tenderness, definite displacement of the cervix, high position of the fetus, signs of fetal death, and identification of an extrauterine mass to be helpful signs and symptoms. Campbell<sup>6</sup> stated that textbooks strive to present the picture of a typical case of misplaced pregnancy, but unfortunately present

TABLE II.

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TYPE AND LOCATION	LENGTH OF GESTATION (WEEKS)	PARITY	GRAVIDITY	AGE	REG. NO.	CASE NO. AND INITIALS
Full-term tubal preg- nancy	Full term	vii	viii	32		1. A. C.
Left interstitial	12	iv	v	32	71-517	2. J. B.
Right interstitial	16	0	i	25	73-336	3. E.M.
Right interstitial	16	0	ii	18	76-165	4. L.C.
Right ampullary	12	i	i	29	85-549	5. E.H.
Right ampullary	15	0	ii	23	76-717	6. J. D.
Right ampullary	12	0	i	32	58-133	7. K. W.
Left ampullary (abing)	12	i	iii	27	88-714	8. L. W.
Right ampullary	12	v	vi	35		9. M. T.
Left ampullary	12	iii	· iv	20	108-543	10. N. B.
Left ampullary	12	0	i	33	134-143	11. M.E.

no definite pathognomonic signs of this condition. These factors must be kept in mind: these patients are all pregnant, and the pregnancy is not implanted in the uterus. Greenhill' stated in his textbook that the abdomen must be opened very carefully because the fetal sac is covered by omentum, intestines, and maybe even the placenta. All are matted together with large, friable blood vessels. The most important act, surgically speaking, is to locate the placenta; and this may be impossible until the sac has been opened and the fetus delivered. When abdominal pregnancy is suspected, x-ray is sometimes helpful in locating the position of the fetus' as well as that of the placenta. The relationship of the fetal back and skeletal parts to the maternal spine sometimes will give a key to the location of the placenta (Fig. 4). In Group A, where the placentas were located posterior to the uterus, the management did not offer a problem. The placenta could be easily removed. Where it was located on the superior portion of the fundus, on the superior portion of the tube, or on the intestinal tract, as in Group B, the management was a definite problem. In one of these cases, the placenta had to be left in situ.

#### TUBAL PREGNANCY

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PREOPERATIVE DIAGNOSIS	POSTOPERATIVE DIAGNOSIS	CHIEF COMPLAINT	RUP- TURED	UNRUP- TURED	REMARKS
Position dystocia transverse lie	Ectopic full- term tubal) pregnancy	Labor pains 14 hr., no progress		X	Complained throughout pregnancy of L.L.Q. pains
Left tubal (inter- stitial) preg- nancy	Same	Left-sided pain, fainting	x		Delivered term fetus vaginally one year after surgery
Ruptured ectopic pregnancy	Ruptured right interstitial preg- nancy	Sudden right-sided pain which became generalized		x	Delivered term fetus spontaneously 6 mo. previously
Ruptured right tubal pregnancy	Ruptured right interstitial preg- nancy	Crampy midline pain, slight bleed- ing, fainting	x		Previous ectopic (left tubal) preg- nancy
Unruptured right tubal pregnancy	Same	Abdominal pain, slight vaginal spotting		x	
Unruptured ec- topic pregnancy	Unruptured right tubal (ampul- lary) pregnancy	Epigastric pain, spotting		Z	Left salpingectomy 9 mo. previously
Ruptured right tubal (ampul- lary) pregnancy	Same	Admitted in shock	X		
Left tubal preg- nancy (ampul- lary-aborting)	Same	"I am 5 mo. preg- nant and not showing"	Abort- ing		
Ruptured right tubal pregnancy	Ruptured right tubal (ampul- lary) pregnancy	Pain in right side	x		
Ruptured left tubal pregnancy	Ruptured left ampullary (tubo-ovarian) pregnancy	L.L.Q. pain, bleeding pelvic mass	x		
Ruptured left tubal pregnancy	Ruptured left tubal (ampul- lary) pregnancy	Pain in left side	x		

In this group of 30 advanced ectopic pregnancies there were two intraligamentous pregnancies. They were not diagnosed preoperatively. They had no definite diagnostic symptoms to call our attention to the diagnosis of intraligamentous pregnancy. The surgical management of these cases was without difficulty, and the placentas were removed without any complications (Table I).

Table II shows that 11 of the cases being reported were tubal pregnancies. These consisted of 8 ampullary pregnancies and 3 interstitial pregnancies. Of the ampullary pregnancies, 5 had symptoms of rupture and 3 were unruptured. One of these was a full-term pregnancy which was delivered alive by laparotomy. This case has been previously reported in the literature by Ross.<sup>6</sup>

Lichtenstein<sup>10</sup> states that if the placenta is located toward the mesosalpinx, the pregnancy has a good chance to continue to a viable age. There was no instance of pregnancy located in the isthmic portion of the tube in our series. Consistent with what is commonly reported, the majority (73 per cent) of

our tubal pregnancies were ampullary. We had no instance of isthmic pregnancy. Due to the small lumen at that point, the tubes usually rupture by the fourth week and we do not attain advanced gestational age as defined in this paper.

Three to 4 per cent of tubal pregnancies are interstitial ones which can develop to a later period of gestation and usually rupture between the fourth and fifth month. There were 3 interstitial pregnancies (27 per cent) in our As usually described, we found the symptoms to be mainly those of shock due to the very profuse bleeding caused by the rich arterial anastomosis involved.

# Summary

1. A study of advanced ectopic pregnancies, as herein defined, occurring at Freedmen's Hospital during the 10 year period 1948 through 1957, is presented.

2. This series comprises 17 abdominal, 2 intraligamentous, and 11 tubal pregnancies.

3. The incidence of ectopic pregnancies in our hospital is very high, 1 in 84 pregnancies; as is the incidence of abdominal pregnancies, 1 in 1,746 pregnancies.

4. An attempt is made to correlate pathogenesis of the abdominal pregnancies to difficulty of diagnosis and surgical management.

5. Those clinical findings which we felt to be most helpful are discussed.

We wish to express our appreciation to Mrs. Naida Willette Page and Mr. Seymour Kaplan for preparation of the drawings and tables.

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# CERVICAL PREGNANCY

Yoshio Ashitaka, M.D., Koreaki Shinohara, M.D., Ichiro Taki, M.D., Masakazu Kosai, M.D., Goro Hirose, M.D., and Katsumi Takayama, M.D., Osaka, Japan

(From the Department of Gynecology and Obstetrics, Osaka University Medical School)

CERVICAL pregnancy is rare. In 1945, Studdiford, reviewing the literature on this entity, described 28 reported cases and 2 of his own. He noted that about half of these cases were backed by pathologic evidence. Goldfine and Mazzanti<sup>2</sup> enumerated 46 reported cases in the literature up to 1957. In the Japanese literature there are no more than 10 case reports of this unusual variety of pregnancy. The present communication deals with a case of cervical pregnancy, the diagnosis and surgical treatment of which were done before the development of serious complications. The extirpated uterus revealed an intact pregnancy of 3 months' size.

# Case Report

S. T., aged 27 years, gravida i, para 0, was first seen in the Gynecological Clinic of the Osaka University Hospital on Feb. 28, 1958, complaining of nausea, vomiting, and vaginal bleeding. The bleeding had begun on January 24 and had occurred intermittently for about 3 weeks. Three years previously she had been pregnant and therapeutic abortion had been done because of hyperemesis. The past history was otherwise irrelevant. Menses had begun at age 16 and occurred every 40 days, lasting for 7 days. She usually had lower abdominal pain before the onset of the menstruation. The last menstrual period was Dec. 4, 1957.

Physical examination revealed a moderately well-developed, well-nourished young woman with a slightly anemic appearance. The heart and lungs were normal. The breasts were tense and showed moderate pigmentation, suggesting early pregnancy. The abdomen was negative. On bimanual examination, the corpus was anteflexed and not unusual in size or consistency. The cervix was soft, fluctuant, and enlarged to the size of a goose egg. The cervical canal was one finger-tip dilated. Between the index finger inserted above the cervical tumor and the fingers on the abdomen a narrow supravaginal cervix was palpated. On speculum examination, the cervix was large and globular, showing fine congested blood vessels and livid coloration. The posterior lip bulged markedly, resulting in ectropion of the endocervix and loss of contour of the external os in its lower half. There was mucous, blood-tinged cervical discharge. The adnexa were normal. No tenderness was present. Exploration of the uterine cavity was not done for fear of causing hemorrhage. The patient was admitted to the hospital with the tentative diagnosis of chorionepithelioma.

On admission, the temperature, pulse, and respiration were normal. Laboratory examination revealed strong positive trophoblast reaction (Shirai) and Friedman's reaction. Titers of the other hormones in the urine were not remarkable for the third month of pregnancy; i.e. total estrogen 338  $\gamma$ , estrone 64  $\gamma$ , estradiol 85  $\gamma$ , estriol 189  $\gamma$ , pregnanediol 3.1 mg. The urinary excretion of 17-ketosteroids was 6.4 mg. per day and of 17-hydroxycorticosteroids 4.1 mg. per day. Tryptophan and histidine reactions of the urine were strongly positive. Blood studies showed: red blood cells 3.8 million, hemoglobin 10.8 Gm., white blood cells



Fig. 1.—Extirpated uterus fixed in formalin. The anterior wall and the amniotic sac are cut in the midline. The narrow isthmus connects the corpus and the cervix, which is larger than the corpus and which bears the products of conception in its posterior wall. The fetal side of the placenta is seen. The cords sits on the left upper quadrant of the placenta. The jellylike mass around the left side of the placenta is a coagulate of amniotic fluid. The endometrium shows decidual hypertrophy. A corpus luteum is seen on the cut surface of the right ovary.



Fig. 2.—Slices of the uterus. These are arranged in a series from the left upper corpus to the right lower cervix. The first, fifth, and last sections are put on the black paper vertically and the others are laid down, showing cut surfaces. The fifth one is the isthmic region. Placental change does not reach this area although decidual change is definite. Sections in the right column reveal remarkable chorionic invasion and hemorrhage (dark spots).

6,000 with 63 per cent polymorphonuclears. The blood pressure was 110/60. An x-ray examination of the chest revealed no significant changes. Slight vaginal bleeding was noted every day after admission but it was not accompanied by cramps or pain.

From the clinical data mentioned above, cervical pregnancy was suspected, although the possibility of chorionepithelioma was not completely ignored. On April 7, total hysterectomy was performed under spinal anesthesia. At operation, the uterus and adnexa were markedly congested. A corpus luteum was found in the right ovary. Fortunately, no profuse bleeding occurred during the course of the operation.

The corpus was somewhat soft and normal in size. The cervix was enlarged, forming a soft ball of about 4 cm. diameter. The products of conception were embedded in the posterior wall of the cervix, covered by a paper-thin cervical tissue. A pinhead-sized area of the amniotic sac was developed on the cervical canal. This may have been due to stripping of thin cervical mucosa which functioned as decidua capsularis. Fifty c.c. of yellow, slightly turbid amniotic fluid was carefully aspirated from the sac. On opening the amniotic sac, it was found that a placenta, 7.5 cm. in diameter and 0.5 cm. in thickness, occupied a large

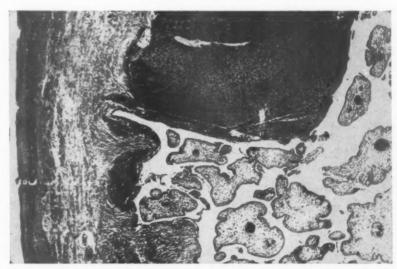


Fig. 3.—Photomicrograph of the section from the tenth slice in Fig. 2. The chorionic invasion reaches the deepest part of the cervix. A thin barrier of connective tissue is demonstrated. Decidual change is not clear in this figure although it is observed in the other fields. In the upper half, blood clot is seen. This may be a sign of abrasion of the anchoring villi

area of the posterior cervix. The embryo was male, 7.5 cm. in body length. The cord, 5.5 cm. long, was attached on the left upper quadrant of the placenta. A narrow, slightly elongated isthmus was differentiated above the tumor of the cervix. The endometrium was thick and soft, revealing definite decidual change. No abnormality was found in the corpus (Fig. 1).

All of the material was fixed in 10 per cent formalin. This was then cut in many slices perpendicular to the long axis of the uterus (Fig. 2). The posterior wall of the cervix was thinned to the utmost, measuring only 1 to 2 mm. Histological examination revealed a normal development of the villi. Decidual formation, however, was very poor. In many places the trophoblasts seemed to be directly in contact with connective tissue. Definite signs of abrasion were observed everywhere. In the mid-posterior wall of the cervix, chorionic invasion reached the deepest part of the cervix. Several bundles of the collagenous fibers mixed with fine muscle fibers remained on the outside of the placental tissue. This may prove the imminence of the rupture of the cervical cyst into the posterior vaginal vault or into the cul-de-sac (Fig. 3). The endometrium of the corpus showed decidual change and glandular hyperplasia.

#### Comment

It is well known that cervical pregnancy often presents serious complications, not infrequently terminating fatally. Early diagnosis and treatment are important. The commonest symptom in the early weeks is vaginal bleeding in varying amounts. It is believed, however, that many of the cases remain undiagnosed and are treated as missed abortions. Many of the reported cases suggest that only careful examination may demonstrate a placental mass attached to the cervix. Many of these cases are clinically confused with chorionepithelioma.

The present case showed initial vaginal bleeding 50 days after the last menstruation. The bleeding was not severe and appeared occasionally for about 3 weeks until the patient first visited the hospital. Cervical pregnancy was strongly suspected by the ballooning and cystic consistency of the cervix, existence of the narrow supravaginal cervix and the small corpus attached on the cervical tumor. Fortunately, the uterus was removed surgically before the development of dangerous complications, which may have been imminent in view of the gross anatomical and histological findings.

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# TUBAL PREGNANCY FOLLOWING HOMOLATERAL SALPINGECTOMY

A Review of 67 Cases Described in the Literature and a Report of 4 New Ones

REMY W. FULSHER, M.D., PORTLAND, ORE.

(From the Department of Obstetrics and Gynecology, University of Oregon Medical School and the Department of Gynecology, Providence Hospital)

THE recurrence of an ectopic pregnancy following homolateral salpingectomy is unusual but may be dramatic in its manifestations.

Because we have been confronted several times with this surgical emergency, we have reviewed the literature for such cases. A number of intriguing considerations were forthcoming. The condition, which was first described by Morfit¹ of St. Louis in 1900, is admittedly rare, yet ten of the authors reporting were able to add several cases of their own (Table I). Moreover, despite the fact that there is agreement on the critical nature of a pregnancy in a tubal remnant with the threat of precipitate shock, there are no recorded data on the mortality resulting from this condition. Then, too, despite the fact that various authors since Lesse² have suggested that this condition could be prevented by routinely performing a complete salpingectomy with cornual resection of the interstitial tube, nevertheless today, 50 years later, the therapy of this type of ectopic pregnancy is still debated.

In this study, we have included 3 cases of ectopic pregnancy following homolateral salpingectomy treated surgically at Providence Hospital in Portland, Oregon, in the past 10 years, and, in addition, a case from the practice of one of the staff of that hospital, which emphasizes the dangerous, even fatal course which may follow.

CASE 1.—Mrs. H. R., a 26-year-old white gravida ii, para i, who had missed a menstrual period 2 weeks previously, was reported by her husband to be complaining of severe pain in the right side of the abdomen. This information was obtained on the telephone, along with the mention that the pain had abated following a "hypo" given by an aunt who was a nurse. The patient's husband was advised to call immediately for an ambulance and have her brought to the hospital. Several hours later, however, the physician received another telephone call, requesting an emergency house call because the patient had suddenly lost consciousness and seemed to have stopped breathing. When the physician arrived, she was dead. An autopsy performed by the coroner's staff revealed that the patient had bled to death following rupture of an ectopic pregnancy in the interstitial remnant of a previously excised tube.

CASE 2.—Mrs. P., No. 57023, a 22-year-old white gravida iii, para i, was admitted to the hospital with the history of a criminal abortion in another state 6 weeks previously,

following which a "button" type of pessary had been inserted into the uterus for contraception. On admission, she stated that she had been "menstruating for ten days." She had experienced severe lower abdominal pain, especially on the right side, for about 6 hours. The blood pressure was 52/28, the pulse 124. She was weak and her skin was cold and clammy.

Her past history revealed an appendectomy and removal of the right tube and ovary 2 years before. The pathological condition found at that time was unknown to the patient.

On examination, the rectus muscles showed moderate splinting with associated marked tenderness in the right lower quadrant. The hemoglobin was 9.9 Gm. per 100 c.c.; sedimentation rate 5 mm, in one hour, leukocyte count 13,600.

At operation, an interstitial pregnancy was found. Only a short stump of the right tube had been left. Two thousand cubic centimeters of blood was removed from the abdominal cavity during the operation. The patient was transfused with 3 units of blood. A wedge resection of the uterine cornu was done, and recovery was uneventful.

CASE 3.—Mrs. O., No. 118703, a 30-year-old white gravida vi, para iii, was admitted for operation with the complaint of abdominal pain of 3 hours' duration. She also complained of faintness and nausea.

The last menstrual period had occurred 3 months previously. There had been no subsequent vaginal bleeding. The patient had been operated on for a ruptured right ectopic pregnancy 9 years before, at which time a salpingo-oophorectomy had been performed.

On admission, the blood pressure was 60/0, pulse 140, and Cullen's sign was present. The abdomen was very tender to palpation. At operation, a fetus of 3 months' gestation was found lying in the abdominal cavity, still attached to the placenta by the cord. The placenta could be seen protruding from a defect in the right cornual area. Approximately 1,000 c.c. of blood was found in the abdominal cavity.

A subtotal hysterectomy was performed because of the large defect in the uterus. The pathological report was: "Placenta in the interstitial portion of the right tube. Placenta had penetrated deep into uterine muscle." The patient was given 7 units of blood during her hospital stay, but she recovered.

CASE 4.—Mrs. T., No. 140374, a white gravida iv, para ii, was first seen at home. She believed that she was about to have a miscarriage. She was visiting in Portland from another city where her physician had told her that she was 5 weeks pregnant. The abdomen was soft and not tender. The cervix was not dilated and there was no vaginal bleeding. The cervix was tender on motion, however, and the uterus was slightly enlarged and softened. A small mass was felt in the area of the right cornu which was exquisitely tender.

The patient volunteered the information that 3 years previously she had had a right tubal pregnancy treated by salpingectomy. It was decided that she should be hospitalized, mainly because Case 1 above is well remembered in this community.

Within a half hour of the patient's admission to the hospital, the blood pressure, which had been normal, dropped suddenly to 40/0. The pulse was then 120 per minute. The abdomen was now very tender and a doughy mass was felt in the cul-de-sac. The hemoglobin was 8 Gm. per 100 c.c. It was obvious that she was bleeding internally and a laparotomy was accomplished immediately.

About 2,000 c.c. of blood was found in the abdomen. Clotted blood and placental tissue were protruding from the right cornu of the uterus, while a small artery on the uterine side, apparently one of the anastomotic branches between the uterine and ovarian arteries, was seen to spurt blood freely (Fig. 1). After the placenta and clots were removed, it was found that there was no communication between the pregnancy and the uterine cavity. It was very easy, however, to push the finger through into the uterine cavity. The edge of the cornual defect was trimmed and the decidua curetted away. Then,

the uterine wall was closed with the same type of closure as is used in a cesarean section. The patient received 4 units of blood during and after operation. She recovered uneventfully.

Three months later, this same patient was seen in the office. She was pregnant again. She went through pregnancy with only a brief episode of painless spotting. A week prior to the expected date of confinement, she was delivered vaginally, following a rapid labor. The child, a male infant, weighed 5 pounds, 14 ounces. The placenta did not separate spontaneously and had to be removed manually. It was inserted over the scar at the side of the previous repair and the uterine wall in that area was found to be extremely thin. There was no perforation, however.

Following the delivery, normal involution of the uterus failed to take place. Persistent uterine bleeding caused severe anemia. It was felt that the uterus was too damaged to bear another pregnancy. A hysterectomy was therefore performed. The specimen confirmed a defect in the myometrium in the right cornual area.

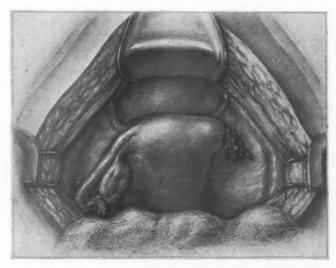


Fig. 1.—Case 4. Ruptured interstitial ectopic pregnancy.

#### Review of the Literature

A review of the literature enabled us to find a total of only 67 cases of ectopic pregnancy following homolateral salpingectomy, as recorded in Table I.

All the patients were between the ages of 22 and 36, with the exception of one who was 41. In only 20 cases was the pathological condition found at original salpingectomy listed as other than ectopic pregnancy, which is in accord with the oft-repeated statement that ectopic pregnancy has a tendency to recur. Many of the patients had had normal term pregnancies between the two ectopic pregnancies, one indeed having had as many as four intervening normal uterine pregnancies. The elapsed time between the original salpingectomy and the second ectopic pregnancy varied from 2 months to 11 years. A cornual resection was performed originally 6 times only, while a tubal stump was left in 33 cases.

The corrective surgical procedures performed at the later operation are also listed in Table I. In some cases, the defect was simply repaired with a few hemostatic stitches. In other cases, attempts were made to remove the interstitial portion of the tube by effecting a cornual resection. At times,

2 years Partial salpin. Excision of cavity in Right 7 weeks

TABLE I. SUMMARY OF DATA FROM PREVIOUSLY REPORTED CASES OF ECTOPIC PREGNANCY FOLLOWING HOMOLATERAL SALPINGECTOMY

											August	1959	
DURATION AND OUT- COME OF PREGNANCY	3 to 4 weeks	2 to 3 weeks	6 months (fetus found under liver)	2 to 3 weeks	10 weeks (fetus in cul-de- sac)	8 weeks	7 weeks	8 weeks	Not listed	6 weeks	4 weeks	6 weeks	3 weeks
SIDE	Right	Left	Right	Left	Right	Left	Right	Right	Left	Left	Left	Right	Right
FINAL OPERATION	Bilateral salpingectomy Right	Excision of pregnancy and repair	Uterus repaired	Total hysterectomy and Left bilateral salpingo- oophorectomy	Subtotal hysterectomy	Excision of cavity in uterus and repair	Excision of cornual end	Defect repaired	Partial salpingectomy, end buried in serosa	Defect repaired	Raw area in cornu closed	Defect repaired, peri-	Total hysterectomy
ORIGINAL OPERATION	Partial salpin- gectomy	Salpingectomy	Partial salpin- gectomy	Partial salpin- gectomy	Salpingectomy	Bilateral cornual		Salpingectomy	Partial salpin- gectomy	Salpingectomy	Salpingectomy	Partial salpin-	Partial salpin-
ELAPSED BETWEEN SALPINGEC- TOMY AND ECTOPIC PREG- NANCY	2 years	6 months	1 year	1 year	6 years	3 months Bilateral		1 year	3 months	5 years	2 years	1½ years	9 years
BLOOD	2,000 c.c.	Large	amount amount	Large amount	2,500 c.c.	1,500 e.e.	Large	1,000 c.c.	Not listed	340 c.c.	Large	750 c.c. 1	Large
CAUSE OF PRE- VIOUS SURGERY	Tubal abscess	Ectopic pregnancy Large amo	Ectopic pregnancy Large amo	Ovarian abscess	Not listed	Vaginal sterili- zation	None. Congenital Large abscence amo	Ectopic pregnancy 1,000 c.c.	Ectopic pregnancy	Ectopic pregnancy 640 c.c.	Ectopic pregnancy Large and	Cystic ovarian	eyst
AGE OF	25	28	Not	30	30	Not listed	53	30	Not	35	30	(1) 28	(2) 28
YEAR	1900	1905	1905	1908	1910	1101	1912	1912	1917	1918	1920	1922	
NAME	Morfit, J. C.1	Hofmeier, M.3	Lesse, F.2	Vineberg, H.4	Campbell, J. L.5	Nacke, W.6	Andrews, H. R.7	Benzel, F.8	Josephson, A.9	Guildal, M.10	Douglas, J.11	Diemer, J.12	

McIntyre, D.13	1922	26	Not listed	Large	3 years	Partial salpin- gectomy	Excision of cavity in uterus	Right	7 weeks
Sigwart, W.14	1922	23	Ectopic pregnancy	Large amount	6 months	Partial salpin- gectomy and peritonization	Resection of cornual area	Right	5 weeks (hydatidi- form mole)
Auvray, M.15	1923	Not listed	Ovarian cyst	Large	9 years	Partial salpin- gectomy	Salpingectomy	Left	6 weeks
Crousse, R.16	1923	30	Not listed	Large	Not listed	Partial salpin- gectomy	Subtotal hysterectomy, left salpingo- oophorectomy	, Right	6 to 8 weeks
Loubat, M.17	1925	22	Ovarian cyst	Large amount	6 months	Partial salpin- gectomy and peritoniza- tion	Salpingectomy	Left	4 to 5 weeks
Hasselblatt, R.18	1926	(1) 27	Ectopic pregnancy 1,000 c.c.	1,000 c.c.	2½ years	Partial salpin- gectomy	Left salpingo-oophorec- Left tomy, right salpin- gectomy, ventral sus- nension	- Left	6 to 8 weeks
		(2) 24	Ectopic pregnancy Small amo	unt	2½ years	Partial salpin- gectomy and peritoniza- tion	Salpingo-oophorectomy	Left	Not listed (tubal abortion)
Petersen, E.19	1926		Ectopic pregnancy Large amo	Large	5 years	Partial salpin- gectomy	Salpingectomy	Left	Not listed
Bierendempfel- Plieck, Erma <sup>20</sup>	1927	60	Not listed	75 e.c.	1 year	Partial salpin- gectomy	Defect repaired	Left	3 to 4 weeks
Guibé, M.21	1928	(1) 29	Ectopic pregnancy	L	1 year	Salpingectomy	Defect repaired	Left	6 weeks
		(2) 31	Ectopic pregnancy	Large amount	3 years	Salpingectomy	Defect repaired	Right	6 weeks
Bello, A.22	1929	59	Ectopic pregnancy	Large	3 years	Partial salpin- gectomy	Subtotal hysterectomy	Right	Not listed
Chabrut, R.23	1929	24	Ectopic pregnancy	Large	5 months	Salpingectomy	Defect repaired	Right	4 weeks
			Ectopic pregnancy	Large	2 years	Cornual resection	Subtotal hysterectomy	Right	4 weeks
Held, E.24	1930	31	Ectopic pregnancy Large amo	Large	4 years	Cornual resection	Cornual resection	Left	3 months

TABLE I-CONT'D

NAME	YEAR	AGE OF		CAUSE OF PRE- VIOUS SURGERY	BLOOD	TIME ELAPSED BETWEEN SALPINGEG- TOMY AND ECTOPIC PREG- NANCY	ORIGINAL	FINAL OPERATION	SIDE	DURATION AND OUT- COME OF PREGNANCY
Naujoks, H.25	1930	(1) 41	Ectopic	Ectopic pregnancy Large amo	Large amount	4½ years	Partial salpin- gectomy	Salpingectomy	Left	3 months (also intra- uterine preg-
		(2) Not listed	(2) Not Parovarian cyst listed		Large amount	9 years	Partial salpin- gectomy and peritoniza- tion	Subtotal hysterectomy	Left	8 weeks
Richardson, L. A.26	1930	Not listed	Ectopic	Ectopic pregnancy Large amo	Large	5 years	Partial salpin- gectomy	Wound closed	Right	6 weeks
Saass, C.27	1930	35	Ectopic	Ectopic pregnancy	Not listed	5 years	Partial salpin Salpingectomy gectomy	Salpingectomy	Left	5 weeks
Ortenberg, A. I.28	1931	25	Ectopic	Ectopic pregnancy Large amo	Large	2 years	Partial salpin- gectomy	Salpingectomy	Left	6 weeks
Schapiro, J. S.29	1933	88	Ectopic	Ectopic pregnancy Large amo	Large amount	7 years	Partial salpin- gectomy	Bilateral cornual resec-Right tion (previously had left salpingectomy)	Right	8 weeks
von Schroeder, O.30	1934	(1) Not listed (2) 21	Ectopic Ectopic	Ectopic pregnancy Large amo Ectopic pregnancy Large amo	Large amount Large amount	2 months 3 months	Partial salpin- gectomy Cornual resec- tion	Bilateral salpingectomy Right (cornual resection) Defect repaired Left	Right Left	3 weeks 8 weeks
Scipiades, E.31	1934	32	Ectopic	Ectopic pregnancy None before	None before opera- tion	3 years	Partial salpin- gectomy	Panhysterectomy	Left	Term baby
Deutsch, J.32	1935	27	Ectopic	Ectopic pregnancy Large	Large	2 years	Salpingectomy	Closure of defect and peritonization,	Right	6 to 7 weeks

TABLE I-CONT'D

NAME	YEAR	AGE OF	CAUSE OF PRE- VIOUS SURGERY	BLOOD	TIME ELAPSED BETWEEN SALPINGEC- TOMY AND ECTOPIC PREG- NANCY	ORIGINAL	PINAL OPERATION	SIDE	DURATION AND OUT. COME OF PREGNANCY
Fairbanks, E. J. <sup>46</sup>	1951	31	Cystic ovary	None	9 months	Cornual resection	Total hysterectomy (left salpingo- oophorectomy)	Right	8 weeks (tubal abortion)
Marbach, A. H.47	1951	30	Ectopic pregnancy 3,000 c.c.	3,000 c.c.	5 years	Partial salpin- gectomy	Defect repaired	Unknown	Unknown 20 weeks
Leverton, J. S.48	1952	53	Chronic salpingo- oophoritis	Moderate amount	6 years	Salpingectomy	Cornual resection	Right	8 weeks
Uriburu, J. V.49	1952	(1) 28	Ectopic pregnancy Large	Large	1 year	Partial salpin-	Defect repaired	Right	8 weeks
		(2) 28	Ectopic pregnancy	Le	3 years	Partial salpin-	Defect repaired	Left	3 months
		(3) 35	Ectopic pregnancy Large amoi	Large amount	1 year	Partial salpin- gectomy	Cornual resection	Left	2 weeks
Saave, J. J.50	1953	37	Ectopic pregnancy Large	. Large amount	2 years	Partial salpin- gectomy	Subtotal hysterectomy	Left	3 months
Ladas, G.51	1955	34	Ectopic pregnancy Small	Small amount	10 years	Salpingectomy	Cornual resection	Left	4 to 6 weeks
Gabriels, A. G., Jr.52	1956	24	Pyosalpinx	None	l year	Salpingectomy	Panhysterectomy	Left	Degenerated placental tissue
Speck, G.53	1956	31	Ectopic pregnancy 2,000 c.c.	2,000 e.e.	1 year	Salpingectomy	Cornual resection	Left	1 to 2 weeks
Conley, D. T.54	1957	(1) 31	Ectopic pregnancy Large	Large	3 years	Salpingectomy	Subtotal hysterectomy	Left	5 months
		(2) 24	Chronic salpingitis 1,500 e.c.	1,500 e.e.	3 years	Partial salpin-	Cornual resection	Right	1 week
		(3) 22	Ectopic pregnancy 2,000 c.c.	2,000 c.c.	2 years	Salpingectomy	Subtotal hysterectomy	Right	4 to 5 weeks

when a partial salpingectomy had been the previous procedure, a salpingectomy consisting of excision of the tubal stump was the operator's choice. Hysterectomy was performed 19 times (28 per cent of the cases).

The duration of pregnancy before rupture varied between one or 2 weeks and 6 months. Three patients died (4.5 per cent mortality). Three had one

subsequent pregnancy.

One case stands out in this series and would truly be the exception precluding any attempt at establishing a rule as the result of this study. In this case reported by Scipiades,<sup>31</sup> a pregnancy developed to term in a tubal stump and resulted in a live birth at laparotomy. The infant survived.

#### Incidence

A survey of the cases of ruptured ectopic pregnancy following homolateral salpingectomy reported individually in the literature gives no index of the frequency of such cases. Mention is made in some previous reports of similar cases which have never been the objects of individual reports, or are insufficiently documented. 55-57

During the past 10 years, 71 cases of ectopic pregnancy, including 3 of the cases herein reported, have been treated at Providence Hospital, Portland, Oregon. Thus, the incidence of ectopic pregnancy following homolateral salpingectomy in this hospital was 4.2 per cent. This high incidence may not be representative of the condition in other hospitals; nevertheless it is significant.

# Etiology

After completing an excellent review of the conditions observed in the cases of recurrent ectopic pregnancy reported up to his time, and after talking personally with many of the operators involved, Hasselblatt¹¹ became convinced in 1926 that in each case of ectopic pregnancy following homolateral salpingectomy recanalization of a tubal remnant had occurred. This observation was later substantiated by many surgeons,⁵³ and is generally upheld in the literature. Even in some cases where an attempt had been made to remove the interstitial portion of the tube by cornual resection during the original salpingectomy, it was later found that the cornual excision had not been successful in removing completely all the tubal epithelium in the uterine cornu.⁴⁰ It appears, therefore, that Hasselblatt's opinion that external migration of the ovum and implantation in interstitial remnants of the excised tube is, in fact, the rule in the condition under study.¹³

Our knowledge of fertilization in human beings may be helped considerably by studying the mechanism in abnormal situations such as these under consideration. External transmigration of the ovum, for instance, was first suggested in 1923 by Dujarrier, <sup>59</sup> who reported a pregnancy in a patient who had had a tube removed on one side and an ovary on the other. Recently, the possibility of external transmigration of the ovum has been strengthened by the observation of pregnancies in imperforate rudimentary horns. <sup>60</sup>

In external transmigration, the ovum is thought to be fertilized in one tube, later to fall back into the abdominal cavity and then travel across the abdomen to the opposite tube. Another concept, perhaps more logical, would have the spermatozoa make their way through one tube and fertilize the ovum directly in the abdominal cavity. This, we believe, is a simple way of explaining the cases of interstitial pregnancy following salpingectomy where homolateral implantation has taken place as is borne out by the fact that the corpus luteum is on the side of the pregnancy. Recently the presence of spermatozoa in the peritoneal fluid and their transmigration have indeed been verified.<sup>61</sup>

Another factor which has not been satisfactorily explained as yet, is the tropism which seems to exist between the ovum and the tubal epithelium. Obviously, in the cases studied here, the ovum can erode its way through a sear into a remnant of the tube. In some cases, such as that reported by Wojcicki,<sup>34</sup> a pregnancy developed in the distal fimbriated remnant, after the

medial portion of the tube had been resected.

Internal migration of the ovum has been suggested by some authors, but it seems illogical to us that the fertilized ovum might travel in a retrograde fashion from the uterine cavity back into the cornual stump. The presence of cilia in the tubal epithelium, along with peristaltic contractions directed toward the uterus, makes this unlikely. Another argument against retrograde implantation of the ovum is the fact that, grossly at operation and in pathological specimens, there was no communication found between the uterine cavity and the pregnancy sac.<sup>37, 40, 44</sup>

# Prophylaxis

Because of the case against internal migration of the ovum and the convincing evidence presented by Hasselblatt, <sup>18</sup> Keller, <sup>58</sup> and others that any small portion of tubal epithelium left in the uterine wall can act as a nidus for further proliferation and recanalization of the surgical scar, it has been generally accepted in the medical literature that, at the time of salpingectomy, deliberate efforts should be made to remove all the interstitial tubal epithe-

lium to prevent homolateral recurrence of ectopic pregnancy.

Table I shows that in 6 instances homolateral recurrence of ectopic pregnancy occurred following cornual resection. In some of these cases, some tubal epithelium was found around the pregnancy, while in others it is doubtful that the original cornual resection had been adequate, as in Nacke's case, where it was performed vaginally. If the cornual resection is thorough and all of the tubal epithelium is removed, there is no reason why a pregnancy should occur in the sear after operation any more than that a pregnancy

should develop in a cesarean section scar.

The procedure described by Falk<sup>56</sup> has been found simple to perform, yet it gives excellent results. An elliptical incision with the long axis directed vertically is made around the base of the tube (Fig. 2, b). The incision is carried through into the uterine wall as far as the uterine cavity to resect the cornual wedge containing the interstitial portion of the tube. In some instances, insertion of a probe through the cornual portion of the tube into the uterine cavity proves very useful to insure complete removal of the tube (Fig. 2, a). Deep catgut sutures may be placed under the area of operation prior to the incision (Fig. 2, c). By tying these over the upper and lower poles of the wound much of the arterial bleeding is immediately controlled. Further shallower sutures may then be placed to reapproximate the periuterine peritoneal covering and stop the superficial bleeding (Fig. 2, d).

Some have tried to bring the round ligament or other structures over the area of the operation for the purpose of reperitonization. This, however, should not be done to cover up a hasty and inadequate repair of the wall of the uterus itself, because too often this round ligament, ovarian ligament, or infundibulopelvic ligament will break loose before healing has taken place,

thus uncovering the defect in the uterus.

The ease with which a cornual resection can be performed varies from one case to another. We verified, on fixed specimens, Ash's<sup>63</sup> observations that the lumen of the tube will often curve upward toward the top of the fundus. Sometimes kinks are present. The length of the interstitial portion is also variable.

Occasionally, especially with an ectopic pregnancy, if the tissues are not handled gently and if the proper precautions are not taken to insure adequate hemostasis, cornual resection may become a rather involved procedure and the results will be unsatisfactory.

In 1928, Guibé, <sup>21</sup> mulling over one of his own cases, decided that "cornual resection complicated unwarrantedly an otherwise simple operation." Chabrut<sup>23</sup> expressed the same opinion at about the same time after operating on a patient who had had an ectopic pregnancy on the same side for the third

time.

We noted with interest that Guibé's opinion was revived recently by Conley and Klieger.<sup>54</sup> Another consideration which has a direct bearing on the advisability of routine cornual resection has been brought up by Hogans and Friedman.<sup>57</sup> This is the possibility of rupture of the uterus in a subsequent pregnancy following cornual resection. Since 1949, 6 such cases have been reported.<sup>57, 64</sup> Many factors may have to do with this eventuality such as the adequacy of the closure and repair following cornual resection, the extent to

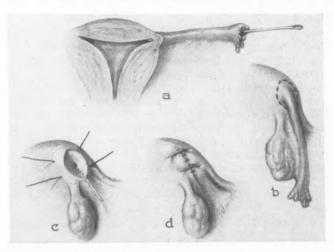


Fig. 2.—Detail of procedure for wedge resection of interstitial portion of tube. a, Probe inserted through tube prior to salping ectomy. b, Incision in cornu will be made along dotted line. c, Deep hemostatic sutures were placed prior to making incision. d, Wound is closed.

which the wound involved the cavum, the weakening caused later by insertion of the placenta over this wound, and the occurrence of a pregnancy before the wound had completely healed. If a cornual resection has been performed carefully, the chances for an uneventful pregnancy and a vaginal delivery

after sufficient healing has taken place are indeed good.

In advising routine cornual resection at the time of salpingectomy many authors seem to have forgotten that our primary concern is to decrease maternal mortality and morbidity. Although cornual resection is desirable to prevent homolateral recurrence of ectopic pregnancy, it is obvious that the condition of the patient at the time of the operation, the type of abnormality encountered, and the chances of leaving a scarred and weakened uterus have to be taken into consideration in the management of the patient. A protracted procedure and increased blood loss might well result in some instances in a stormy postoperative course and even an occasional death.

At Providence Hospital, where much of the gynecological surgery is done by general practitioners and general surgeons, a cornual resection was performed only 8 times in 68 cases of ectopic pregnancy in the past 10 years; salpingectomy was performed 53 times, and partial salpingectomy 7 times. No doubt, cornual resection could have been performed safely more often, and there seems to be very little justification for a partial salpingectomy which results in the creation of a "tubal stump." Nevertheless, there are times when a simple salpingectomy, accomplished by separating the Fallopian tube at the point where it enters the uterine wall, is the procedure of choice.

#### Treatment

A review of the literature shows that the surgical treatment of a ruptured pregnancy in an interstitial remnant has been varied. Roughly there were three categories: simple closure of the tubal wound with hemostatic sutures; excision of the defect and reconstruction of the uterine wall; and, hysterectomy, subtotal or total, with or without adnexal surgery.

Such lack of uniformity in the treatment of this condition reflects the opinion expressed by Bret<sup>65</sup> about the treatment of interstitial pregnancy in general: "One should not have a rigid attitude but should be eelectic and adopt the type of treatment applicable to the individual case." In some cases, conservative surgery involving complete excision of the hemorrhagic tissue in the cornual end of the uterus and repair of the uterine wall can be performed. Occasionally a hysterectomy may have to be resorted to, when the defect in the uterus appears beyond repair.

We do not agree with some who follow Keenan's<sup>66</sup> advice that "in interstitial pregnancy a subtotal hysterectomy should be performed routinely because it is a safer and faster procedure." Table I shows that 19 hysterectomies were performed. In only one case<sup>38</sup> was a hysterectomy performed because the operator was afraid that a simple repair would not accomplish adequate hemostasis. In most instances, the radical surgery was performed because there were associated lesions in the uterus or the remaining tube. Four times<sup>23, 39, 40, 42,</sup> the defect was so large that repair would have left the organ functionally too weak. The postoperative recovery in patients in whom the defect was simply repaired was uneventful.

### Obstetrical Considerations

What is the obstetrical future of the patients who fall within the scope of this paper?

We have already mentioned the possibility of complete rupture of the uterus following cornual resection. In addition, Malfetano<sup>67</sup> reported an incomplete rupture at cesarean section in a patient who had earlier in life had a salpingectomy and cornual excision for interstitial pregnancy. We agree with von Vegh<sup>40</sup> that, as a rule, it is safe to let patients be delivered vaginally who give a history of previous cornual resection. Rupture of the uterus should, however, be kept in mind and exploration of the uterus to rule out an incomplete rupture should be performed at the termination of the third stage of labor.

In patients who have a tubal pregnancy following homolateral salpingectomy, the defect in the uterine cornu is usually quite extensive. Débridement of the jagged edges of the wound and repair have proved adequate surgical treatment. One might wonder, however, whether these patients should be encouraged to become pregnant again.

To our knowledge only 3 women have borne live children following two homolateral ectopic pregnancies. One of these patients was our own (Case 4 above). This woman, who had two daughters, was extremely desirous of preserving her childbearing function in the hope of having a boy. von

Schroeder,30 many years ago, was faced with a similar situation. In both instances, vaginal delivery was followed by a hysterectomy, in von Schroeder's case because of rupture of the uterus and intra-abdominal bleeding, and in ours because of incomplete rupture of the uterus and subinvolution with persistent vaginal bleeding. The third patient (Burger's<sup>43</sup> case) was delivered by cesarean section.

The meager experience available to date on the obstetrical future of a patient whose uterus has been repaired after excision of a tubal pregnancy following homolateral salpingectomy shows that it is possible for these patients to carry another pregnancy to term successfully. Labor and delivery are not without danger, however, in these women whose uteri were extensively damaged.

We feel that you Schroeder's case and ours would have been managed more safely if Burger's choice, a cesarean section without labor, had been preferred to a vaginal delivery. It is also possible that a cesarean hysterectomy might have a place in the management of these patients.

# Summary and Conclusions

- 1. Four cases of interstitial pregnancy following homolateral salpingectomy are reported.
- 2. A detailed review of the literature available on this condition is presented.
- 3. The etiology and treatment of the condition are discussed, along with its effect on the obstetrical future of the patient.
  - 4. The present status of cornual resection is reassessed.

We wish to thank Dr. William M. Wilson for allowing us to publish Case 1.

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# ENDOCRINE STUDIES IN TWO INSTANCES OF TERM ABDOMINAL PREGNANCY

ALVIN M. SIEGLER, M.D., SIDNEY ZEICHNER, M.D., IRVING RUBENSTEIN, M.D., ELEANOR Z. WALLACE, M.D., AND ANNE C. CARTER, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology of the Beth-El Hospital and the Department of Medicine, The State University of New York, College of Medicine at New York City)

EXTRAUTERINE pregnancy proceeding to term is an unusual obstetrical entity. Two cases of term secondary abdominal pregnancy, occurring on the same obstetrical service, provided an opportunity to study the effects of a retained placenta on the urinary excretion of chorionic gonadotropin hormones and on certain indices of adrenocortical function.

# Case Reports

Case 1.—Mrs. L. C., a 30-year-old Negro woman, para 1-0-0-1, was first examined on Aug. 2, 1956, in the twenty-second week of gestation. Her most recent menses had occurred on Feb. 19, 1956. The previous medical history was normal; a pregnancy in 1942 had resulted in a term spontaneous delivery of a normal 8 pound infant.

At the time the patient was first seen, physical examination was within normal limits with the uterus enlarged to the size of a 20 weeks' gestation. The patient had had a normal antepartum course with an 11 pound weight gain and blood pressure within normal limits until the thirty-fourth week of pregnancy, at which time urinalysis revealed 1 plus protein. The fetus was felt to be in a transverse position. At term, Dec. 10, 1956, the patient entered the hospital with mild abdominal pain and stated that fetal movements had ceased 2 days prior to admission. Physical examination disclosed the fetus to be in a transverse lie with the vertex in the right iliac fossa. Blood pressure was 135/110. There was no pretibial edema. Three plus proteinuria was present. Proteinuria and elevation of the blood pressure persisted for the 48 hours after admission; the patient complained of increasing lower abdominal pain. There was moderate distention of the abdomen and an external version failed. Roentgenological study of the abdomen revealed the fetus in a transverse position with the dorsum over the inlet and the vertex in the right iliac fossa. An abdominal pregnancy was suspected and a laparotomy was performed 48 hours after admission. A term intra-abdominal pregnancy was found; the fetus was dead and was removed after puncture of the membrane. The placenta was adherent to the small intestine and to the superior leaf of the broad ligament; the umbilical cord was ligated and cut; the uterus was enlarged to the size of a 10 weeks' gestation. The right tube and ovary were normal and the left adnexa were adherent deep in the cul-de-sac. The estimated blood loss was 50 ml. The patient had an uneventful postoperative course and was discharged 9 days after the operation with a normal blood pressure but persistent 1 plus proteinuria.

Autopsy of the fetus, which weighed 3,400 grams and measured 40 cm. in length, revealed maceration of the skin but no congenital abnormalities.

The patient was readmitted to the hospital 56 days after the operation because of gross hematuria and lumbar pain, associated with a temperature elevation of 24 hours'

duration. The abdomen was soft; a nontender, firm, fixed midline mass arose from the pelvis 8 cm. above the symphysis pubis. Urine culture revealed Aerobacter aerogenes and Escherichia coli which were sensitive to Furadantin and Gantrisin. The patient responded well to these antibiotics and was given a transfusion of 500 ml. of whole blood. The fever and discomfort promptly subsided and the patient was discharged 3 weeks after admission. An intravenous pyelogram revealed a right hydroureter.

Her first menses post partum occurred on March 14, 1957, 3 months after the laparotomy, and during the following months menses were irregular. Lactation had never occurred. Basal body temperature graphs and endometrial biopsies revealed that the episodes of vaginal bleeding were anovular. Urinary gonadotropins were elevated to 63 I.U. per 24 hours on Dec. 3, 1957. Because of the persistence of the abdominal mass, a laparotomy was performed one year post partum, on Dec. 10, 1957. A cyst, 10 to 15 cm. in diameter, was found which appeared to be in the right broad ligament. The uterus was normal in size but had a small posterior cervical myoma. The ovaries were quite small, 2 cm. at their largest diameter. The left Fallopian tube was normal and the right tube was attenuated over the cystic mass. There was some omentum adherent to the cyst, which was enucleated intact, and a myomectomy was performed. Histological study of the tissue revealed ghost forms of chorionic villi. The cyst fluid gave a negative Friedman test and no chorionic gonadotropin activity was found. The patient made an uneventful recovery. She was lost to follow-up and further menstrual history is not available.

Case 2.—Mrs. C. R., a 32-year-old white woman, para 2-0-1-1, was admitted to the hospital on Nov. 8, 1956, at 22 weeks' gestation, with right-sided abdominal pain and obstipation of 2 days' duration. Her last menses had occurred on May 21, 1956, and the expected date of confinement was Feb. 28, 1957. Past history revealed that in the third month of gestation the patient had been hospitalized with abdominal pain radiating to the right shoulder and had been treated for a presumed attack of acute cholecystitis.

Physical examination at the November, 1956, admission revealed a blood pressure of 118/68 and pulse of 108. The abdomen was tender throughout and rebound tenderness was most marked in the right paraumbilical area. An abdominal mass was palpable to the level of the umbilicus. The upper abdomen was moderately distended and soft; some distended loops of bowel were seen through the abdominal wall. The fetal heart was present in the right lower quadrant. A diagnosis of peritonitis secondary to a ruptured viscus was made. One hour after admission the patient suddenly developed profound shock. She was transfused with 1,500 ml. of whole blood and improved; intestinal decompression was begun. The next day a roentgenogram of the abdomen revealed moderate distention of the small intestine, with no gas seen in the large bowel distal to the hepatic flexure. A 6 month fetus was in the transverse position. After initial improvement, the patient developed intense jaundice on the fourth hospital day but this subsided during the next 7 days. On the eleventh hospital day, cholecystograms showed an nonfunctioning gall bladder. The fetal heart rate was normal throughout the hospitalization. The remainder of her antepartum course was uneventful except for the persistent transverse lie of the fetus. An abdominal pregnancy was suspected and a hysterogram, on Feb. 11, 1957, in the thirty-eighth week of gestation, showed a term fetus in the upper abdomen. A small uterine cavity was opacified but the usual uterine shadow about the fetus was absent.

The patient was admitted to the hospital and a laparotomy was performed on Feb. 12, 1957. The fetus was found within a thickened extrauterine amniotic sac. The placenta was attached to the posterior superior aspect of the uterus and the parietal peritoneum on the posterior abdominal wall. A normal living female child who weighed 3,200 grams was removed after amniotomy. The umbilical cord was tied and cut; the placenta was left in situ. The estimated blood loss was 50 ml. The postoperative recovery was uneventful and the patient was discharged on the seventh postoperative day.

The infant had no congenital abnormalities and growth and development have been normal.

The first postpartum menses occurred on April 5, 1957, 5 weeks after laparotomy. By the tenth postoperative week, the abdominal mass had receded to the size of a 4 months' gestation, however, the patient continued to have episodes of mild lower abdominal pain and diarrhea. In July, 1957, 5 months post partum, she had an exacerbation of lower abdominal pain accompanied by fever and enlargement of the previously described abdominal mass. An incision was made near the midpoint of the laparotomy scar and approximately 750 ml. of purulent fluid mixed with necrotic tissue was extruded. Pathologic examination of the extruded tissue revealed amorphous and calcified material but no formed elements. The fistulous tract closed spontaneously during the following weeks. The second menstrual period occurred on Aug. 29, 1957, 5 months after the initial episode of vaginal bleeding, and her menses have been regular since that time.

#### Methods

Urinary chorionic gonadotropins, 17-hydroxycorticosteroids, and 17-ketosteroids and plasma 17-hydroxycorticosteroids were measured at intervals following removal of the intra-abdominal fetus in each patient. Twenty-four hour urine specimens were collected and refrigerated without added preservative. Urinary 17-ketosteroids were determined by a modification of the method of Drekter, Pearson, Bartezak, and McGavack.¹ Levels for normal females range between 6 and 14 mg. per 24 hours. Urinary and plasma 17-hydroxycorticosteroids were determined by the method of Silber and Porter as modified by Peterson.² Normal females excrete 3 to 9 mg. of 17-hydroxycorticosteroids in the urine per 24 hours. Plasma 17-hydroxycorticosteroids taken between 8 and 9 A.M. in normal individuals range between 3 and 28 mg. per 100 ml. Adrenocortical responsiveness was evaluated by the measurement of plasma and urinary 17-hydroxycorticosteroid and urinary 17-ketosteroid levels before and after a 6 hour intravenous administration of 25 units of ACTH in 500 ml. of 5 per cent glucose in water.

Urinary chorionic gonadotropins were determined by a modification of the method of Behnken, Lloyd, and Hughes.<sup>3</sup> Normal women in the last trimester of normal pregnancy usually exercte between 1,000 and 8,000 I.U. per 24 hours by this method.

#### Results

The results of the endocrine studies performed are given in Table I. Urinary chorionic gonadotropins remained positive in Patient L. C. at levels of 900 I.U. per 24 hours up to 28 days following laparotomy and removal of the intra-abdominal fetus. Thirty-five days postoperatively chorionic gonadotropin excretion was not measurable.

In Patient C. R., levels of chorionic gonadotropins were positive at 38,000 per 24 hours 30 days post laparotomy and were not detected at 36 days.

The amount of 17-ketosteroids and 17-hydroxycorticosteroids excreted in the urine tended to be in the subnormal to low normal range throughout the postpartum period of observation in Patient L. C. and were normal throughout in Patient C. R. Plasma 17-hydroxycorticosteroids were uniformly within the normal range in both patients. In patient L. C. there was a suggestion of slow decline from a high normal level on the fifth day to a mean normal level on the thirty-fifth day. Responses of the plasma 17-hydroxycorticosteroids to ACTH were within normal limits when tested on the thirty-fifth postoperative day in Patient L. C. and on the thirty-sixth postoperative day in Patient C. R.

#### Comment

In some cases of term abdominal pregnancy, a functioning placenta is left in the abdomen after death or operative removal of the fetus. The presence of this unusual circumstance in the 2 patients reported permitted evaluation of the influence of the placenta alone on certain adrenocortical steroid alterations associated with pregnancy.

TABLE I. ENDOCRINE STUDIES IN PATIENTS L. C. AND C. R.

	STU 17-0	SMA DIES OHCS		URINAR	Y STUDI	ES	
DAY POST PARTUM	CON-	POST ACTH	17-ohcs (MG./24 HR.)	17-KS (MG./24 HR.)	GONAD	OTROPINS (24 HR.)	CREATININE (GM./24 HR.
Patient L. C		ACIH	(MG./24 HR.)	(MG./24 HR.)	(1.0./	24 HR.)	(GM./24 HA.
2	·.—		1.4	5.4	Pos. Neg.	695 2,780	0.875
4 5 6 7	27.5		3.7	5.5	2105.	_,	0.890
6	2110		1.9	2.8			0.661
7			4.7	4.4			0.825
14					Pos.	430	01020
					Neg.	1,720	0.942
21	25.7		4.0	1.2		,	1.149
28	19.7		3.0	6.4	Pos.	900	
					Neg.	3,600	1.280
35	16.4	48.1	4.5	2.5	Neg.	650	0.932
36			23.9	8.2			0.954
65			0.2	2.2			1.111
170			1.1	5.0	Neg.	698	0.990
200			1.6	4.2	Neg.	425	0.910
363*					Neg.	1,340	
Patient C. I	2.—						
30			4.4	8.4	Pos. Neg.	38,800 194,000	0.854
36	26.9	56.7	19.4	13.1	Neg.		0.692
78	_0.0	5511	4.2	8.1	Neg.		0.732

\*Patient's serum (1 ml. per animal) and abdominal cyst fluid (2 ml. per animal) negative for chorionic gonadotropins.

The duration of function of retained extrauterine placentas is variable. Reports in the literature, as summarized in Table II, have described positive Friedman or Aschheim-Zondek tests persisting for as long as 53 days as well as negative tests at 5 days in abdominal pregnancies following death or delivery of the intra-abdominal fetus.<sup>4-10</sup>

Continued placental activity in the 2 patients reported here was reflected by persistence of measurable levels of urinary chorionic gonadotropins for at least 28 days in Patient L. C. and 30 days in Patient C. R. In Patient L. C. levels of 900 I.U. per 24 hours 28 days post partum were compatible with involution of the placenta. Titers of 38,800 I.U. per 24 hours 30 days post partum in Patient C. R. were higher than those usually encountered in the third trimester of pregnancy.

Pregnancy is accompanied by a number of changes in the metabolism of adrenocortical steroids, the significance and etiology of which have been the

subject of much recent interest. A slight to moderate increase in urinary corticosteroids, measured as Porter-Silber chromogens and 17-ketogenic steroids, occurs during pregnancy. Urinary 17-ketosteroids, when measured by the Zimmermann reaction, consistently show increases during pregnancy. Plasma 17-hydroxycorticosteroid levels become elevated by the third trimester of pregnancy and the rise in plasma 17-hydroxycorticosteroids, induced by stimulation with ACTH, becomes greater than normal. These phenomena are accompanied by a delay in the clearance of hydrocortisone from the peripheral blood.

TABLE II. REPORTED ENDOCRINE STUDIES IN ABDOMINAL PREGNANCIES

CASE AND REFERENCE	YEAR	DURATION OF PREGNANCY	RESULTS OF STUDIES AND NO. OF DAYS AFTER OPERATION
Ware and Main <sup>4</sup>	1934	Term	Positive Friedman test at 36 days
Eisaman and Zeigler <sup>5</sup>	1935	Term	Negative Aschheim-Zondek test at 8 days
MacGregor <sup>6</sup>	1937	Term	Negative Friedman test at 5 days
Ware and Main?	1938	Term	Positive Friedman test at 47 days
Lull <sup>8</sup>	1940	Term	Positive Friedman test at 6½ weeks; negative when repeated with dilutions
Branscomb <sup>9</sup>	1947	Seven months	Positive Aschheim-Zondek test at 53 days; negative Aschheim-Zondek test at 58 days
Weinberg, Salz, and Funaro <sup>10</sup>	1958	Term	Positive "pregnancy test" at 26 days; negative at 54 days
Present study	1958	Term	Elevated urinary chorionic gonadotropins at 28 days; negative at 35 days
	1958	Term	Elevated urinary chorionic gonadotropins at 30 days; negative at 36 days

Increasing interest centers on the possible role played by the placenta in producing the alterations in adrenocortical metabolism which occur in normal pregnancy.

The work of Johnson and Haines,<sup>14</sup> Berliner, Jones, and Salhanick,<sup>15</sup> and Little and Rossi<sup>16</sup> suggests that some plasma corticosteroids in pregnancy may be derived from the placenta. Another possibility is that the changes in adrenocortical steroids and their metabolism in pregnancy are secondary to effects of noncorticosteroid hormones secreted by the normal placenta. Estrogens have been shown to cause elevations in plasma 17-hydroxycorticosteroid levels associated with a delay in the clearance of hydrocortisone from the peripheral blood.<sup>17-18</sup> The similarity to the findings in pregnancy is striking.

In neither of the 2 patients, who both had evidence of continued function of the retained placentas, was there clear-cut evidence of elevation of the plasma 17-hydroxycorticosteroids; nor were increases in either urinary 17-ketosteroids or corticosteroids found. Stimulation with corticotropin resulted in normal rises in the concentration of plasma 17-hydroxycorticosteroids in both subjects.

By virtue of its ectopic location and vasculature, the abdominal placenta probably cannot be considered identical in function with the normal uterine placenta. Since the 2 patients were not studied antepartum it cannot be certain that elevation of plasma or urinary steroids, or hyperresponsiveness to

ACTH was present at any time during the course of their abdominal preg-The placenta, therefore, cannot be eliminated as the factor responsible for the alterations in adrenocortical steroid metabolism in pregnancy on the basis of the observations recorded here.

Several clinical points concerning the postpartum courses of both patients warrant mention. In Patient L. C. a cystic abdominal mass persisted unchanged for one year following removal of the abdominal fetus and placental remnants and finally required surgical removal. In Patient C. R. a living normal child was obtained at laparotomy despite apparent episodes of tubal rupture at the sixth week of gestation and placental separation at 6 months' gestation. The fate of the placenta in this patient was liquefaction necrosis and slough through a fistulous tract 5 months post partum.

# Summary

- 1. Two cases of term secondary abdominal pregnancy have been reported.
- 2. Urinary chorionic gonadotropin assays indicated continuing placental activity for at least 28 and 30 days after removal of the intra-abdominal fetuses in the 2 patients.
- 3. No elevation of plasma 17-hydroxycorticosteroids, urinary 17-ketosteroids, or urinary 17-hydroxycorticosteroids, or increase in responsiveness to ACTH stimulation was found in either patient during the period of continued placental function.

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# THE RENAL HANDLING OF SODIUM AND WATER IN NORMAL AND TOXEMIC PREGNANCY\*†

RUSSELL R. DE ALVAREZ, M.D., GLORIA E. BRATVOLD, B.S., AND GEORGE T. HARDING, M.D., SEATTLE, WASH.

(From the Department of Obstetrics and Gynecology, University of Washington School of Medicine)

VER since the first systematic observation of the urinary constituents in L normal pregnancy by Winckel<sup>12</sup> in 1865, much investigation has been focused on the kidney, its function, and its response to extrarenal factors in an attempt to discover and to explain the etiology of the exact renal mechanisms operating in pregnancy toxemia. Whether the kidney plays a primary or secondary role in the etiology of toxemia of pregnancy is not known, but some derangement in renal function is certainly responsible for a part of the toxemic process. The advent of newer methodology has made it possible to demonstrate definite alterations in the physiology of fluid and electrolyte balance, not only in normal pregnancy but in pregnancy toxemia as well, and to show that these shifts occur in association with changes in renal hemodynamic mechanisms.

Practically all reports indicate the occurrence of a positive water balance during normal pregnancy with delayed excretion of water load and/or an increase in the extracellular fluid volume. 1-3, 5-10, 12 That an accompanying positive sodium balance occurs in normal pregnancy and is exaggerated in toxemia of pregnancy4, 15 is equally well recognized. Along with this, an elevation in urinary steroid excretion is known to occur during late normal pregnancy as well as in pregnancy toxemia and may be related to increased renal tubular reabsorption of sodium. Since some of the steroids excreted in urine may represent products of metabolic transformation rather than the true internal secretion,13 and since they could result from renal, hepatic, or placental disturbances, caution must be exercised in the interpretation of their significance. Perhaps some of the conclusions reached are based on indirect evidence through the interpretation of a decreased excretion of urine sodium as being synonymous with increased urinary steroid exerctions, without measurement of the actual total steroids which are being exerteed. The inference is often carried even further to the point of interpreting the steroid influences as being responsible for the increased renal tubular reabsorption of sodium and thus the positive water and sodium balance of pregnancy.

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In a series of renal clearances reported by us during normal pregnancy, a significant decrease from the elevated glomerular filtration rate noted in the first trimester began early in the second trimester and persisted through the remainder of pregnancy. The average value of GFR for the period from the twenty-ninth to the fortieth week of pregnancy was 105 ± 8.93 c.c. per minute (corrected to 1.73 square meters of body surface). We have suggested that the positive water and sodium balance of normal pregnancy is related to a decrease in GFR with an attendant increase in tubular reabsorption of sodium at this duration of pregnancy. As a result of the decreased sodium load presented to the tubules, greater efficiency in the reabsorption of this electrolyte should be permitted. On theoretical grounds, a decrease in GFR of 1 c.c. per minute for 24 hours should increase the tubular reabsorption of water by 1,440 c.c., assuming that the decreased GFR is associated with constant tubular reabsorption. No change in total body water should occur if no new water is added. Thus, with the fall in filtration, a decrease in the excretion of water occurs. In the presence of a constant sodium concentration of the extracellular fluid and a constant intake of sodium, and with the decreased GFR, a daily sodium reabsorption of 202 mEq. (.140 mEq./e.e.  $\times$  1,440 e.e./24 hr. = 201.6 mEq./24 hr.) should result. While theoretical calculations based on isolated values of GFR have been cited, no published reports based on actual data have, to our knowledge, appeared. Page 16 calculated the hypothetical glomerular filtrate of water and sodium for nonpregnant patients, normal pregnant women, and patients with pregnancy toxemia in an attempt to explain the mechanism of edema formation in toxemia of pregnancy. He felt that the edema could be due to an alteration in glomerular filtration rate or to an alteration in the tubular reabsorption of sodium or to both. Inasmuch as our studies of serial renal hemodynamics, serum electrolytes, 24 hour sodium excretion, and 24 hour water excretion were simultaneously determined, we felt it might be possible to provide a quantitative evaluation of the roles played by these factors in the production of positive sodium and water balance not only in normal pregnancy but also in patients with toxemia of pregnancy.

# Subjects and Materials

A total of 100 renal function studies were performed. These consisted of simultaneous inulin clearance, para-aminohippurate clearance, creatinine clearance, serum electrolyte concentration, urine electrolyte excretion, and water excretion. In 10 normal pregnant patients, 20 studies were performed at varying intervals during the last trimester of pregnancy and 10 following delivery. The remaining 70 studies were performed on patients with toxemia of pregnancy (1 each) during the last trimester of pregnancy or in the postpartum priod. In the toxemic group 25 patients were diagnosed as having mild pre-eclampsia; 35 had severe pre-eclampsia, and 10 had eclampsia. The final classification of type of toxemia was based upon antepartum, immediate postpartum, and late puerperal findings, as well as upon data derived, when possible, during the pregravid period.

#### Methods

The renal function tests were begun at 8 a.m., with the patient in a fasting state, 2 hours following the ingestion of 600 c.c. of water. The function tests in the normal pregnancy and toxemic pregnancy groups were identical. The details of the methodology of renal hemodynamics and measurement of electrolytes have been previously described. Because the clinical status of some of the toxemic patients was so critical at the time of admittance to the

hospital, study at the time of maximum positive sodium and water balance was precluded and therefore delayed until the patient's condition permitted. Where practicable, however, patients were tested shortly after admittance to the hospital, while in positive balance, and prior to the institution of therapy. The sodium intake in patients with pregnancy toxemia under therapy averaged 30 mEq. per day. The water intake for patients with pregnancy toxemia averaged 4,000 c.c. per day and was accurately measured. The estimated average intake of water for the normal pregnant patients was 2,000 c.c. Accuracy of collections of 24 hour urine output was checked by the measurement of creatinine. Each renal clearance study required at least 120 minutes for completion with approximately 6 serial blood and urine samples obtained during each of the tests.

# Results

Glomerular filtration rate is expressed as the volume of the ultrafiltrate of plasma which passes through the renal glomeruli in cubic centimeters per minute. The rate of inulin clearance is considered to be the measurement of glomerular filtration rate. Table I illustrates the antepartum and postpartum GFR values occurring in normal and toxemic pregnancies. The value in our normal nonpregnant control group averaged 108 c.c. per minute—almost identical to the value established by Smith.<sup>14</sup> Except for the antepartum patients with normal pregnancy, where 20 serial GFR determinations were performed on 9 patients during the last trimester of pregnancy, one determination per patient was performed in each of the other groups. The average GFR during the last trimester of normal pregnancy was 105 c.c. per minute but rose to 130 c.c. per minute in the immediate postpartum period. This value represents a significant increase in GFR (p>.01) over the level noted in the last trimester of normal pregnancy.

TABLE I. GLOMERULAR FILTRATION RATE

		ANTE PARTUM			POST PARTUM	
PREGNANCY CLASSIFICATION	NO.	MEAN AND STANDARD ERROR (C.C./MIN.)	σ	NO.	MEAN AND STANDARD ERROR (C.C./MIN.)	σ
Normal pregnancy*	20	104.9 ± 8.93	26.80	10	129.5 ± 2.27	7.20
Mild pre-eclampsia	13	$89.38 \pm 5.69$	20.49	12	114.0 ± 8.46	29.26
Severe pre-eclampsia	7	$65.86 \pm 10.38$	27.41	28	107.6 ± 6.47	34.24
Eclampsia	2	$34.50 \pm 25.57$	36.06	8	$66.8 \pm 13.93$	39.42

\*Normal nonpregnant female = 108 c.c. per minute.

Of the 70 patients with pre-eelampsia or eclampsia, 22 were studied during the last 7 weeks of gestation and are classified in Table I. The GFR in patients where mild pre-eelampsia occurred ante partum averaged 89 c.c. per minute. This represents a decrease of 16 c.c. per minute below the value found among normal pregnant patients at this same duration of pregnancy. The more severe the pre-eclamptic process, the lower the rate of glomerular filtration. The values averaged 66 c.c. per minute in severe pre-eclampsia and 35 c.c. per minute in patients with eclampsia. The antepartum GFR in eclamptic patients was significantly lower than the antepartum values for normal pregnant women and for mildly pre-eclamptic women. The GFR in severe pre-eclampsia and eclampsia revealed no statistically significant differences (p>.05).

Forty-eight patients with pre-eclampsia or eclampsia were studied between the first and the twenty-first day post partum. Twelve had mild pre-eclampsia, 28 had severe pre-eclampsia, and 8 had eclampsia. As in the antepartum group, the decrease in GFR was proportional to the severity of the toxemia. The value in mild pre-eclampsia averaged 114 c.c. per minute, 108 c.c. per minute in severe pre-eclampsia, and 67 c.c. per minute in eclampsia. The values of GFR in both mild pre-eclampsia and in severe pre-eclampsia were significantly elevated during the postpartum period when compared to values in the antepartum period for the same type of toxemia. Although the average postpartum GFR for those patients with eclampsia was almost double the average of the antepartum values, no valid statistical comparison is possible because of the small number of patients available for study in the antepartum period. When comparing the postpartum GFR values for the various classes of pregnancy, those in patients with eclampsia revealed GFR values not only significantly lower than those for normal pregnancy (p>.001) but also lower than those in patients with mild and severe pre-eclampsia.

Renal Water Reabsorption.—Renal water reabsorption represents that per cent of the total fluid filtered by the renal glomeruli which is reabsorbed by the renal tubules over a 24 hour period. This calculation implies a constant rate of filtration throughout the entire 24 hour period. While it has been proposed that the GFR is subject to diurnal variation, recumbence, sleep, emotions, and many other factors, Sirota, Baldwin, and Villarreal<sup>11</sup> do not agree with these claims. Predicated on the concept of possible diurnal variations, we felt justified to use the total 24 hour volume rather than the value obtained during the renal test in order to calculate the renal water reabsorption. If the renal function test alone were used it could be considered as having been run at a time when renal water reabsorption was significantly lower than at other portions of the 24 hour period.

By applying the average GFR of 108 c.c. per minute found in our nonpregnant female group and the average 24 hour urine volume of 1,160 c.c. in the same group, to a formula:

#### RENAL TUBULAR REABSORPTION OF WATER PER CENT (TRAH20)

- A. GFR (c.c./min.) x 1,440 (min./24 hr.) = Renal Water Load per day (c.c./24 hr.)
- B. (A) Urine volume (c.c./24 hr.) = Renal Water Reabsorption per day (c.c./24 hr.)
- $\times$  100 = Renal Tubular Water Reabsorption per day (TRA<sub>H2O</sub>), per cent,

a theoretical normal nonpregnant female water reabsorption value of 99,25 per cent was calculated:

#### SAMPLE CALCULATION-TRAHOO

- A. 108 c.c./min.  $\times$  1,440 min./24 hr. = 155,520 c.c./24 hr.
- B. 155,520 c.c./24 hr. -1,160 24 hr. urine volume = 154,360 c.c./24 hr.
- C.  $\frac{154,360}{155,520} \times 100 = 99.25\% \text{ TRA}_{\text{H}_20}$ .

The influence of the reduced GFR on the tubular reabsorption of water in the eclamptic patient is exemplified in the following formula:

#### CALCULATION-TRAH2O ECLAMPSIA

- A. 10 c.c./min.  $\times$  1,440 min./24 = 14,400 c.c./24 hr.
- B. 14,400 c.c./24 hr. 3,110 c.c. (24 hr. vol.) = 11,290 c.c./24 hr.
- C.  $\frac{11,290}{11,120} \times 100 = 78.40\% \text{ TRA}_{\text{H}_20}$ .

The values for renal water reabsorption during the antepartum and postpartum periods in normal and toxemic pregnancies are shown in Table II. It will be noted that the values for normal pregnancy are slightly lower than those in the normal nonpregnant woman. The slight reduction in renal water reabsorption in the postpartum period as compared to the antepartum values seems to be related to postpartum diuresis. In the 62 patients with pregnancy toxemia, one renal function study was carried out in each patient and the renal water reabsorption for patients with mild pre-eclampsia and for those with eclampsia was almost equal. The average antepartum water reabsorption for the severe pre-eclampsia group was 94.85 per cent which represented a highly significant depression of water reabsorption when compared to the value during normal pregnancy. During the postpartum period, 43 patients with toxemia of pregnancy were studied; the majority were classified as having severe pre-eclampsia-eclampsia. The postpartum values for renal water reabsorption in mild and severe pre-eclampsia averaged 97.44 and 97.58 per cent, respectively, while those for the eclamptic group averaged 91.96 per cent.

TABLE II. RENAL TUBULAR REABSORPTION OF WATER

		ANTE PARTUM			POST PARTUM	
PREGNANCY CLASSIFICATION	NO.	MEAN AND STANDARD ERROR (%)	σ	NO.	MEAN AND STANDARD ERROR (%)	σ
Normal pregnancy	20	99.08 ± 0.11	0.32	9	99.01 ± 0.23	0.66
Mild pre-eclampsia	11	$96.87 \pm 0.47$	1.55	10	$97.44 \pm 0.23$	0.73
Severe pre-eclampsia	6	$94.85 \pm 1.51$	3.11	28	$97.58 \pm 0.25$	1.33
Eclampsia	2	$96.26 \pm 2.67$	3.77	5	$91.96 \pm 3.63$	8.14

The increase in renal water reabsorption from the antepartum period to the postpartum period was highly significant in the group with severe pre-eclampsia. The postpartum renal water reabsorption for mild pre-eclampsia was found to be significantly depressed when compared to the renal water re-absorption value for normal pregnancy during the postpartum period. There was no statistically significant difference between the postpartum renal water reabsorption values in normal pregnancy and the postpartum values in severe pre-eclampsia (Table VI). Those in the postpartum patients with eclampsia were significantly lower than the values observed in normal pregnant patients during the postpartum period. This value for eclampsia proved to be not only significantly lower than the postpartum value for patients with mild pre-eclampsia, but also represented a highly significant depression when compared to the severe pre-eclampsia group.

TABLE III. RELATIONSHIP OF URINE FLOW TO TUBULAR REABSORPTION OF WATER

		ANTE P	ARTUM			POST P	ARTUM	
PREGNANCY	U	.F.	TR	A <sub>H2O</sub>	U	.F.	TR	A <sub>H2O</sub>
CLASSIFICATION	24°	RENAL	24°	RENAL	24°	RENAL	24°	RENAL
Normal pregnancy	0.93	1.23	99.08	98.55	1.26	4.16	99.01	96.66
Mild pre-eclampsia	2.34	1.31	96.87	97.73	2.79	3.73	97.44	95.91
Severe pre-eclampsia	2.92	2.19	94.85	95.97	2.35	3.70	97.58	95.44
Eclampsia	0.59	0.68	96.26	97.41	2.25	2.15	91.96	94.61

Urine flow, in cubic centimeters per minute, during the renal function test (Table III) in every group, except eclampsia, was slightly reduced during the total 24 hour period. The reduction in the normal pregnant patients may well be due to the fact that these patients were not encouraged to change their usual habits in order that representative data could be obtained from the patients' ordinary and usual mode of living. On the other hand, many of the hospitalized patients with toxemia of pregnancy, at the time of these studies, were in the initial stages of the treatment regimen, which included the reduction of electrolytes and an increased fluid intake. This probably accounts for the increased urine flow for the 24 hour period in the toxemia group, as compared to that in normal pregnancy. However, no parallelism between the rate of urine flow in cubic centimeters per minute and the tubular

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reabsorption of water could be shown. Rates of urine flow in antepartum patients with toxemia were generally lower during the time of the renal function study than were those calculated from the total 24 hour urine excretion. Changes in rates of urine flow during the period covered by the actual renal test and the rate for a given 24 hour period showed no proportionate relationship in tubular reabsorption of water. In the postpartum period, urine flow was increased in each group of patients during the renal function study. This increase in urine flow was generally associated with a decrease in the tubular reabsorption of water in postpartum patients; this is as it should be and reflects normal behavior of tubules in normal and toxemic pregnancy. While the same trends could not be shown when considering urine flow based on the 24 hour excretion, the severe degrees of toxemia demonstrated an inverse relationship of tubular reabsorption of water to the changes in calculated urine flow from the antepartum to the postpartum period.

# Renal Sodium Reabsorption .-

The per cent of the total sodium filtered by the renal glomeruli and reabsorbed by the renal tubules in 24 hours constitutes renal sodium reabsorption. Because it has been found<sup>11</sup> that a definite increase in tubular reabsorption of sodium also occurs at night, it was felt that the total 24 hour urine sodium excretion, rather than that obtained during the renal function test alone, would permit a more equitable measure for calculating tubular sodium reabsorption. The formula for the renal sodium reabsorption is:

# RENAL TUBULAR REABSORPTION OF SODIUM PER CENT (TRANA)

- A. Plasma (Na\*) (mEq./1,000)  $\times$  Renal Water Load (c.c./24 hr.) = Na Load to Kidney per day (mEq./24 hr.)
- B. (A) Urine Na Excretion per day (mEq./24 hr.) = Renal Na Reabsorption per day (mEq./24 hr.)
- C.  $\frac{(B)}{(A)} \times 100 = \text{Renal Na Reabsorption per day (TRA}_{Na})$ , per cent.

The determination of the hypothetical renal sodium reabsorption for the normal nonpregnant female is:

# SAMPLE CALCULATION-TRANA

- A. 108 e.e./min.  $\times$  1,440 min./24 hr.  $\times \frac{140}{1,000} = 21,772.80$  mEq./24 hr.
- B. 21,772.80 114.50 24 hr. urine Na Excretion = 21,658.30 mEq./24 hr.
- C.  $\frac{21,658.30}{21,772.80} \times 100 = 99.47\% \text{ TRA}_{Na}$ .

The values computed in 65 patients studied during normal and toxemic pregnancy in the antepartum and postpartum periods are illustrated in Table IV. It will be noted that no significant difference in mean renal sodium reabsorption occurred when the antepartum and postpartum periods of normal pregnant patients were compared.

TABLE IV. RENAL TUBULAR REABSORPTION OF SODIUM

		ANTE PARTUM			POST PARTUM	
PREGNANCY CLASSIFICATION	NO.	MEAN AND STANDARD ERROR (PER CENT)	σ	NO.	MEAN AND STANDARD ERROR (PER CENT)	σ
Normal pregnancy	8	99.54 ± 0.42	0.72	4	99.72 ± 0.08	0.16
Mild pre-eclampsia	7	$99.50 \pm 0.18$	0.48	10	$99.75 \pm 0.05$	0.17
Severe pre-eclampsia	4	$99.60 \pm 0.16$	0.33	25	$99.58 \pm 0.08$	0.40
Eclampsia	2	$99.12 \pm 0.49$	0.69	5	$98.28 \pm 1.43$	3.21

Thirteen patients with toxemia of pregnancy, 7 with mild pre-eclampsia and 6 with severe pre-eclampsia-eclampsia, were studied during the last 2 months of pregnancy. The data for the normal and toxemic pregnancy during the antepartum period fell within the range of  $99.36 \pm .24$  per cent; consequently, there was no significant difference between normal pregnant patients and those with toxemia of pregnancy during the antepartum period. Likewise in the postpartum group, there was no significant difference in renal tubular sodium reabsorption between postpartum normal or toxemic pregnancy. On the basis of our data, calculations, and statistical analysis, there was no significant difference in renal sodium reabsorption between any of the pregnancy groups compared, normal or toxemic, during the antepartum or postpartum period. All values for these groups fell within the range of  $99.00 \pm .75$  per cent. The significance (p = 0.02) of the difference in the mean of factors studied in the various patient groups is shown in Tables V and VI.

TABLE V. ANALYSES OF GFR, TUBULAR WATER REABSORPTION, AND TUBULAR SODIUM REABSORPTION
(COMPARISON OF ANTEPARTUM PERIOD WITH POSTPARTUM PERIOD)

	ANTEPARTUM VS. POSTPARTUM PERIOD			
PREGNANCY CLASSIFICATION	GFR	WATER	SODIUM	
Normal pregnancy	0.01	> 0.05	> 0.05	
Mild pre-eclampsia	0.02	> 0.05	> 0.05	
Severe pre-eclampsia	0.01	0.001	> 0.05	
Eclampsia	> 0.05	> 0.05	> 0.05	

TABLE VI. ANALYSES OF GFR, TUBULAR WATER REABSORPTION, AND TUBULAR SODIUM REABSORPTION
(COMPARISON AMONG THE VARIOUS CLASSIFICATIONS OF PREGNANCY)

PREGNANCY	(	FR	WATER		SODIUM	
CLASSIFICATION	AP	PP	AP	PP	AP	PP
NP vs. MP	> 0.05	> 0.05	0.01	0.001	> 0.05	> 0.05
NP vs. SP	0.05	> 0.05	0.05	> 0.05	> 0.05	> 0.05
NP vs. E	0.01	0.001	0.05	0.02	> 0.05	> 0.05
MP vs. SP	0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
MP vs. E	0.01	0.01	> 0.05	0.01	> 0.05	> 0.05
SP vs. E	> 0.05	0.01	> 0.05	0.001	> 0.05	> 0.05

# Analysis of Data

Patients were grouped as normal pregnant (NP), mild pre-eclampsia (MP), severe pre-eclampsia (SP) and eclampsia (E); the groups were further subdivided into their respective antepartum and postpartum periods. In order to determine, in the normal pregnant group, whether or not significant differences occurred with the duration of pregnancy, the data for the last trimester of pregnancy were studied in 3 groups: (1) twenty-ninth to thirty-second week of gestation; (2) thirty-third to thirty-sixth week, and (3) thirty-seventh to fortieth week of pregnancy. The results of our statistical analysis showed no significant difference among these three groups. Since the experimental data of these subdivisions of the last trimester of pregnancy revealed no significant difference, all data from the twenty-ninth to the fortieth week of gestation were considered as a single antepartum unit. All postpartum patients with a normal pregnancy were studied within the first 5 days following delivery.

Inasmuch as all undelivered patients who developed antepartum toxemia were studied between the thirty-third and fortieth weeks of pregnancy, it was not necessary to subdivide this group as was done in the normal pregnancy group. Thus, the data in the antepartum patients with toxemia may be compared with the data derived between the twenty-ninth and fortieth weeks in

the normal antepartum group. Because of the many physiologic alterations which occur during the early puerperium, the patients with postpartum toxemia were divided into three different groups (1 to 5 days post partum, 1 to 10 days post partum, and 11 to 21 days post partum) in an attempt to determine whether or not the findings in each of these time periods were significantly changed. No statistically significant difference was noted between the "1 to 5 days post partum" group and the "1 to 10 days post partum" group. Therefore, these two groups were combined as a "1 to 10 days post partum" group for comparison with the "11 to 21 days post partum" group. Here, again, the data in these two groups revealed no significant difference in values. Thus, we were able to simplify statistical comparisons and analyses of the antepartum and postpartum phases of the patients with normal and with toxemic pregnancies (Table V). The statistical analyses among the various classifications are noted in Table VI. The final groupings are listed as follows:

NP-A—Normal pregnancy, ante partum (29 to 40 weeks' gestation)
NP-P—Normal pregnancy, post partum (1 to 5 days post partum)
MP-A—Mild pre-eclampsia, ante partum (33 to 40 weeks' gestation)
MP-P—Mild pre-eclampsia, post partum (1 to 20 days post partum)
SP-A—Severe pre-eclampsia, ante partum (35 to 40 weeks' gestation)
SP-P—Severe pre-eclampsia, post partum (1 to 21 days post partum)

E-A—Eclampsia, ante partum (35 to 40 weeks' gestation) E-P—Eclampsia, post partum (1 to 15 days post partum)

## Comment

The drop in GFR begins at approximately the twenty-second week of normal pregnancy and continues to a level essentially the same as that of the normal nonpregnant value until term. It would seem that the positive water and sodium balances noted in normal pregnancy might well result from a primary and continued depression of GFR. The exaggerated positive balance of water and sodium in patients with pregnancy toxemia would also seem to result from the even more marked depression of GFR. When normal pregnancy is compared with toxemia of pregnancy and when mild degrees of toxemia are compared with severe pre-eclampsia and eclampsia, a direct relationship seems to exist between the severity of the pregnancy toxemia and the depression in glomerular filtration. However, the statistically significant increase in renal water reabsorption, so often postulated as occurring in toxemia of pregnancy, is not confirmed in our patients. It is entirely possible, however, that increased reabsorption may well have occurred prior to admittance or during the phase of oliguria. The data obtained by us probably reflect post hoc results rather than measurement of derangements in physiologic processes when they were actually happening. On the contrary, our studies reveal a significant decrease in water reabsorption in toxemic patients during both the antepartum and postpartum periods. This decrease in tubular water reabsorption would seem to imply a decreased tubular reabsorption of sodium in toxemia of pregnancy which was not seen in normal pregnancy. It is necessary, however, to consider that the majority of the patients with toxemia of pregnancy, at the time of the renal function study, had been placed for short periods of time on a reduced sodium intake (approximately 30 mEq. of sodium chloride per day) and an increased intake of fluid. In the face of such a therapeutic regimen, a compensatory increase in tubular reabsorption should theoretically take place in an attempt to conserve sodium. The decrease in GFR should also increase the efficiency of sodium reabsorption in the proximal tubules, reducing the sodium load to the distal tubules. With the smaller quantity of sodium to be reabsorbed, it would seem that a greater opportunity might be presented for almost complete reabsorption of the administered sodium; however, our data show no significant change in sodium reabsorption in either the normal or the toxemic patient during pregnancy.

The decrease in water reabsorption during toxemia of pregnancy would seem to indicate, in contrast to current concepts, a decrease in reabsorption of sodium. Just as the pattern in diabetes insipidus represents marked impairment of facultative reabsorption of water, the decreased water reabsorption among our patients with toxemia of pregnancy might be attributed to the ability of the tubules to pass the glomerular filtrate along but not to elaborate it. While therapy could be implicated as a factor in the reduction of tubular reabsorption of water and electrolytes, it is not the sole factor. Therapy results in a combination of decreased sodium intake and increased fluid intake, resulting in a decrease in osmolarity of the extracellular fluid, stimulating volume receptors and inhibiting the supraoptic and paraventricular hypothalamic osmoreceptors. This suppresses posterior pituitary elaboration of antidiuretic hormone, decelerating the reabsorption of water in the renal tubules. Unfortunately only indirect assessment of these phenomena is possible inasmuch as actual objective measurements of ADH are fraught with considerable inaccuracies.

In our own laboratory we have undertaken objective measurements of aldosterone and simultaneous Na/K ratios. Our data indicate an increase in average aldosterone excretion in the urine during normal pregnancy. The increase in average aldosterone excretion as pregnancy advances is roughly paralleled by a decrease in urinary Na/K ratio. We have noted, in work currently under study, that the Na/K ratio in normal pregnancy is similar to the curve noted by us for GFR in normal pregnancy. Thus, sodium excretion parallels GFR, which probably accounts for the positive sodium balance in normal pregnancy.

Although aldosterone alters the urinary Na/K ratio independent of GFR and filtered sodium load, there is evidence that depression of the ratio does not progress beyond a maximum rate of secretion of aldosterone. In adrenalectomized and intact rats the urinary Na/K ratio reaches a minimum value at 0.5  $\mu$ g per kilogram with no further depression following the administration of doses above that amount. The data from our laboratory indicate a fair degree of correlation between urinary aldosterone excretion and urinary Na/K ratio when urinary aldosterone excretion is between 5 and 20  $\mu$ g per 24 hours. In the last trimester of pregnancy, the urinary excretion of aldosterone averages about 30  $\mu$ g per 24 hours. This suggests the possibility that in late pregnancy the values approach those resulting in maximum urinary Na/K ratio depression. This is further supported by the curve of urinary Na/K ratio which, in our group of normal pregnant patients, reached its lowest value in late pregnancy. No difference has been observed between aldosterone excretion in our normal pregnant patients and that in our patients with severe pre-eclampsia-eclampsia.

These observations seem to be consistent with the findings that little difference exists between the renal sodium reabsorption fractions of our normal and of our toxemic pregnancies. In the early postpartum period, aldosterone excretion falls to a level below which there is also poor correlation between urinary aldosterone excretion and urinary Na/K ratio. At this time, the Na/K ratio returns rather promptly toward normal in both normal and toxemic pregnancies, suggesting that aldosterone influence may be minimal in both cases. The observation that the sodium reabsorption fraction is the same in both normal and toxemic pregnancy in the late antepartum and early postpartum periods is more difficult to explain.

The fate of a large proportion of the filtered load would seem to depend upon cellular metabolism particularly in the proximal renal tubules but with further modification of the filtrate in the distal segment. This connotes ion

exchange mechanism with an increased tubular rejection of sodium in the proximal tubule, an increase distal tubular exchange for potassium, and a resultant progressive decrease in the Na/K ratio as pregnancy advances. The ion exchange mechanism would imply intracellular rather than extracellular processes. The inverse relationship of Na/K to aldosteronuria suggests the possibility that this process is under the control of the adrenal cortex or is the result of possible elaboration of the steroid by the placenta or the fetal adrenal.

## Conclusions

1. On the basis of our data, a significant decrease in renal water reabsorption occurs in patients with pregnancy toxemia during the late antepartum period and in the puerperium when compared to normal pregnant women. That the same thing occurs in treated toxemia would suggest intact tubular responses.

2. No significant difference in renal sodium reabsorption was noted in any of the pregnant groups when they were compared, normal or toxemic, during the antepartum or postpartum period. In normal and in toxemic pregnancy the mean and renal sodium reabsorption fraction is 99.00 ± .75 per cent in the late antepartum and the postpartum periods.

3. The positive sodium and water balance of normal pregnancy and the exaggerated values in pregnancy toxemia seem related to a progressive depression of GFR.

4. The elaboration of progressively increasing aldosteronuria during normal and toxemic pregnancy probably contributes significantly to the occurrence of a positive sodium balance as reflected by the inversely proportionate Na/K ratio.

5. It would seem that the kidney alone may be responsible for most of the modifications of sodium and fluid volume in normal and toxemic pregnancy and that general metabolic, placental, and additional humoral influences also contribute to the alterations of renal function.

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# THE PATHO-MECHANISM OF LATE PREGNANCY TOXEMIA AND OBSTETRICAL HEMORRHAGES

II. Placental Site and Venous Drainage of the Pregnant Uterus

J. Bieniarz, M.D.,\* Gdansk, Poland

(From the Department of Obstetrics and Gynecology, First Women's Clinic, Medical Academy, Gdansk)

IN A previous communication (Part I<sup>8</sup>) a marked contrast between the clinical pictures of placenta previa and of pre-eclampsia-eclampsia was reported. In 25,000 pregnancies there were 95 cases of placenta previa and 125 cases of severe toxemia. The blood pressure was usually low and there was no proteinuria or edema in the placenta previa cases, whereas high blood pressure, severe proteinuria, and marked edema were characteristic of toxemia. A statistical analysis of these results has shown that this contrast in clinical symptomatology could not have arisen by chance and there must be an essential cause for it. The search for this cause seemed promising because it might, eventually, be correlated with the cause of toxemia and hemorrhage itself.

Based on clinical observations which are to be related, it seems probable that the development of an extensive uteroplacental circulation in advanced pregnancy, its hemodynamic impact on systemic circulation, and humoral influence upon the metabolism may be responsible for the development of both toxemia and hemorrhage.

Pregnancy is associated with the introduction of what must be regarded as an entirely new viscus into the general circulation—the placenta.<sup>28</sup> The development within a short time of a considerable uteroplacental circulation amounting to several hundred cubic centimeters of blood flow per minute<sup>3, 11, 32-34</sup> must impose a special stress upon the hemodynamics of the pregnant woman. The placenta is, besides, the most important endocrine organ in the pregnant organism.<sup>35</sup> The influences of its humoral factors, hormones, and enzymes, are the strongest with their greatest concentration upon the organs met first on the drainage pathways of the uteroplacental circulation. With the development of such a circulation on a low pelvic level in placenta previa the possible hemodynamic (physical) and humoral (chemical) effects might well be entirely different from those of a high-seated placenta with the development of its circulation on a high abdominal level. With different drainage directions of a high- and of a low-seated placenta, different organs

<sup>\*</sup>Present address, Seccion Fisiologia Obstetrica, Facultad de Medecina, Avenida General Flores, 2125, Montevideo, Uruguay.

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are flooded by the strong current of uteroplacental blood, thus producing contrasting hemodynamic and humoral effects. This might well explain the observed contrast in clinical symptomatology between placenta previa and eclampsia.

The correctness of this assumption depends wholly on two facts: (1) whether high-implanted placentas are really more frequent in toxemia; and (2) whether an entirely different direction of drainage can be observed from a high- as compared with a low-seated placenta.

The purpose of the present investigation was to answer these questions.

# Material and Methods

Observations of the placental site and the gross vascular pattern were carried out during 183 cesarean sections in the First Women's Clinic, Medical

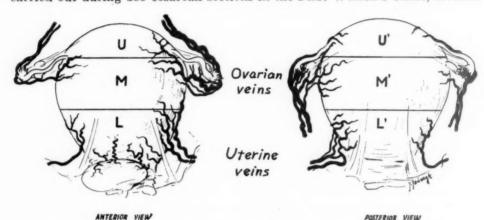


Fig. 1.—Anterior and posterior view of the uterus with venous vascular patterns visible during cesarean section as well as regions of placental site:

 $\begin{array}{lll} \text{Anterior wall } \left\{ \begin{array}{ll} U, & \text{upper pole site} & U' \\ M, & \text{midsegment site} & M' \\ L, & \text{lower pole site} & L' \end{array} \right\} \text{Posterior wall} \end{array}$ 

Academy, Gdansk. It was an unselected series of consecutive cases treated during the years 1956-1957. The vascular pattern was compared with similar findings during laparotomies on nonpregnant women, as well as with findings in 15 autopsies on pregnant or early puerperal women carried out in four neighboring districts. This gave the opportunity of broadening the observations on the whole vascular system.

There were 63 primigravidas and 120 multiparas, the ages ranging from 19 to 46 years. The indications for the operation were: dystocia 73, hemorrhage 56, toxemia 10, fetal distress 31, miscellaneous 13.

After the abdomen was opened and the abdominal wall gently lifted with retractors, special attention was paid to the state of the exposed uterine vasculature; the observations were limited almost exclusively to veins because of their overfilling, prominence, and good visibility. Arteries could not have been observed because of their inaccessibility.

The uterine vasculature was closely watched on the anterior surface of the uterus, above the bladder and in Retzius' space, below the bladder after incision of the peritoneum and shifting of the bladder downward, and medial to the round ligaments (Fig. 1). All these veins had a definite downward direction, toward the uterine and iliac veins, forming thus tributaries of the lower caval circulation. Lateral to the round ligament only the inner branches coursed in the same downward direction, the more lateral ones usually turning upward toward the pampiniform plexuses and ovarian veins leading high up to the level of the renal circulation. This high drainage route could be better observed after the delivery of the child by lifting the closed uterus up out of the abdominal cavity. The vascular pattern of the lateral and posterior walls of the uterus, the pampiniform plexuses, and the ovarian pedicles of the infundibulopelvic ligaments could be seen. In some cases the deeper regions of the pouch of Douglas, the sacrouterine ligaments, and the region of the ureters were inspected for possible connections of uterine vasculature with neighboring viscera.

It was thought that the vascular pattern, the state of overfilling of veins estimated by their prominence, broadness, and tortuosity in different directions might, to a certain measure, give evidence of the general direction of the uteroplacental venous drainage. The state of the veins in the lower region which seemingly discharged downward to the uterine and iliac veins was noted and compared with the state of the pampiniform plexuses and ovarian veins leading up toward the renal and abdominal visceral circulation. The observations were recorded by hand-sketches and occasionally by photographs.

The exact site and extent of the placenta within the uterine cavity were noted by intrauterine palpation immediately after the delivery of the child. The height of the implantation was recorded as U—upper pole site, M—midzonal site, and L—lower pole site, after the respective region of the anterior uterine wall on which the main mass of the placenta was found, or U', M', and L', with the placenta on the respective region of the posterior uterine wall (Fig. 1). The placental site was identified in all 183 cesarean sections and correlated in each case with the signs of toxemia or hemorrhage, if present. Toxemia and hemorrhage were classified according to accepted criteria for diagnosis and severity.

#### Results

Placental Position in Toxemia, Hemorrhage, and in Normal Pregnancy.— The results are shown in Table I and diagrammatically represented in Fig. 2. There were found:

# 65 High implantations:

- 20 predominantly fundal implantations (UU', U, U', MUU', MU'U') (Fig. 1)
- 45 high implantations in the body of the uterus (MU, MU')

# 118 Low implantations:

- 67 midsegment implantations in the uterine body (M, M')
- 31 low implantations in the uterine body (ML, M'L')
- 20 implantations in the lower uterine segment (MLL', M'L'L, LL')

# Total 183

There were: 3 cases of eclampsia, 44 cases of pre-eclampsia, 20 cases of essential hypertension, 14 cases of abruptio placentae, 58 cases of normal pregnancy,\* and 44 cases of placenta previa.

Of 20 fundal placentas, 12 were in the pre-eclampsia-eclampsia groups with 4 others in the essential hypertension and one in the abruptio placentae groups. Three fundal placentas were found in the normal group in

<sup>\*</sup>There were no signs of toxemia or hemorrhage although these cases had some other pathologic state as an indication for cesarean section, e.g., dystocia or fetal distress.

Table I. Correlation Between Placental Site and Severity of Toxemia or Hemorrhage. Frequency Distribution of Placental Positions in Each Category

_		-07			-	-	L PLACE	NOMBLAN	NORMAL	NORMAL FLACENTAE SION
_	7 :	7	MOD-	MOD-	MOD- MOD-	MOD-	MOD- MOD-	PREG- MOD- MOD-	PREG- MOD- MOD-	SVIA PREG- MOD- MOD-
SIA   MILL		_	SPAIR	_	EDATE MILL ERALE	EDATE MILL ERALE	MILL ENAIE MILL ENAIE	MILL ENAIE MILL ENAIE	A MANUE SHALE MILL ENAIE	THE WANCE MILL ENGIR MILL ENGIR
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-							1	1	1	1
				<b>6</b> 3	<b>0</b> 1	631	61	631	67	61
						1	1	1	1	1
ଦୀ				-	1	1	1	1	1	1 1
17		_	1	3 1	61	1 2 3 1	1	1	1	1
-		1	1	3 1	1 3 1	1 3 1	6 1 3 1	6 1 3 1	6 1 3 1	6 1 3 1
C)				60	33	2 3 3		63	63	63
1		1	1	5 1	2 5 1	63	1 2	16 1 2	16 1 2	16 1 2
							1	2 1		
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									1	1 1
35		8	co	17 3		17	9 17	5 9 17	58 5 9 17	13* 58 5 9 17

TABLE IA.

LACENTAL SITE	ABNORMAL PREGNANCY: PLACENTA PREVIA, ABRUPTIO PLACENTAE, HYPERTENSION	NORMAL PREGNANGY	PRE-ECLAMPSIA- ECLAMPSIA	TOTAL
High Mid-low	17	13 45	35	65 118
Total	75	58	50	183

multiparas who showed no toxemic or hemorrhagic symptoms. Of the 3 patients with severe pre-eclampsia, 2 had fundal placentas and the remaining one a high corporeal position. In the 6 cases of moderate pre-eclampsia the placenta was fundal in 3 and a high corporeal one in one further case. There was not a single case of severe or moderate pre-eclampsia with a low-seated or previa placenta (Table I).

The high position of the placenta in the upper segment of the uterine body (UM, U'M') was most frequent in the mild pre-eclampsia group. This placental position was found in 20 cases of pre-eclampsia, one of eclampsia, 8 of essential hypertension, 4 of abruptio placentae, and in 10 normal preg-

nancies.

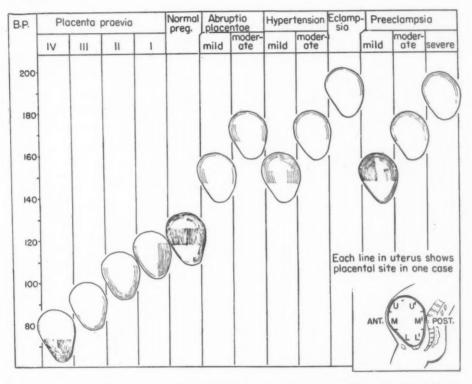


Fig. 2.—Correlation between placental site and severity of toxemia or hemorrhage (diagrammatic).

The mid-zonal position of the placenta was most frequently found in the normal pregnancies (38 M and M' out of 58 cases) and the group with abruptio placentae (8 out of 14 cases). It was far less frequent in the pre-eclampsia-eclampsia group with one case of eclampsia and 11 of pre-eclampsia-eclampsia

out of 50 (Table I).

Of the 31 low corporeal placentas (ML, M'L') 7 belonged to the normal pregnancy group whereas 24 were diagnosed as placenta previa. The 20 placentas implanted predominantly in the lower segment (L, L') were all in the placenta previa group. Of the 44 patients with placenta previa 3 developed mild symptoms of pre-eclampsia raising the number of toxemia cases to 50; in 5 cases, all fourth-degree placenta previa, there was some albuminuria present (Table I).

Statistical Analysis.—From the clinical point of view it would be most interesting to compare the frequency of high-seated placenta in a group of pregnant women showing toxemia and that in a group with normal pregnancies. In 50 cases of toxemia there were as many as 35 fundal and upper segment placentas comprising 70 per cent, whereas there were only 15 (30 per cent) mid-zonal and lower segment placentas, including 3 cases of precelampsia from the placenta previa group (Tables I and IA). In 58 cases of normal pregnancy there were, on the other hand, 13 higher situated placentas constituting 22.4 per cent and 45 (77.6 per cent) mid-zonal and lower segment placentas. The difference between the two proportions of high-seated placentas in women with toxemia and in those with normal pregnancy is 70 per cent minus 22.4 per cent which equals 47.6 per cent. The standard error of the difference between the two proportions is:

$$\sqrt{\frac{70 \times 30}{50} + \frac{22.4 \times 77.6}{58}} = \sqrt{42 + 29.97} = \sqrt{71.97} = 8.49$$

The observed difference between the two proportions is more than twice the value of the standard error of the difference 47.6:8.49 = 5.61. One might, therefore, draw the conclusion that the two observed percentages of high-seated placenta in women with toxemia and in those with normal pregnancy

differ by more than might be expected to be due to chance.

These comparisons, as interesting as they are from the clinical point of view, are not statistically independent; therefore the probability values associated with these statistics do not have the conventionally accepted meaning. The differences are so great, however, that there can be little doubt as to the existence of the difference, regardless of their exact probability values. We may, anyhow, make a statistical analysis of our results within the orthogonal sets of independent comparisons: (1) pre-eclampsia-eclampsia versus all other groups of pregnancy, normal and abnormal; (2) pre-eclampsia-eclampsia versus normal pregnancy and versus all other groups of abnormal pregnancy; (3) pre-eclampsia-eclampsia versus all abnormal groups of pregnancy.

1. The placental position is a descriptive category difficult to express quantitatively. The significance of the frequency of high-seated compared with mid- and low-seated placentas in pre-eclampsia-eclampsia versus all other groups might therefore well be expressed by Pearson's chi-square test. The calculation of  $\chi^2$  gives the value 35.56 when n=1; the probability P from Fisher's tables is less than .01, and the unequal distribution of placental positions in toxemia compared with all other groups of pregnancy is therefore

unlikely to occur by chance.

2. Similarly the calculation of  $\chi^2$  shows a significant difference between the placental positions in normal pregnancy and those in pre-eclampsia-eclampsia and placental positions in all other abnormal pregnancies:  $\chi^2 = 35.54$  when n = 2 and P is less than .01. The far greater frequency of high-seated placentas in women with toxemia compared with that in other groups of pregnancy, normal and abnormal, is statistically significant and unlikely to have arisen by chance.

3. Among the abnormal pregnancies there is a very highly significant difference between the placental positions in the pre-eclampsia-eclampsia group and all other pathologic pregnancies, with  $\chi^2 = 29.37$ , n = 1, and P

less than .001. It is therefore unlikely to occur by chance.

The Influence of the Height of Implantation of the Placenta Upon the Uterine Vascular Pattern.—Of the 183 cesarean sections only 138 could be

analyzed with sufficient reliability as to the state of uterine vascularity; the observations of the first 45 operations could not properly be taken into account because of the unavoidable incompleteness and inaccuracy during the time when the final method and classification were being worked out.

The drainage of the uteroplacental circulation has shown a marked tendency to higher routes through the pampiniform plexuses and ovarian veins from high implanted placentas (Fig. 3, U, U'). Only in 7 cases some veins of the lower drainage route were also visible, but there was not a single case observed of an exclusive prominence of lower vessels in this group of high-seated placentas. In placenta previa there was, on the contrary, a marked prominence of the lower circulation vessels, suggesting a tendency to a discharge of uteroplacental blood downward through the uterine and hypogastric

		U 🦱	ט' ( )	M (m)	M' ()	L @	L' 🔘	
h	4	24	8	6	4	0	0	42
?	$\bigcirc$	1	0	1	12	1	3	18
0	50	1	1	5	7	1	1	16
v	红	5	0	7	13	2	8	35
d	R	0	0	3	6	4	14	27
		31	9	22	42	8	26	138

U = upper pole anterior wall placenta

U' = upper pole posterior wall placenta

M = medium segment anterior wall placenta

M' - medium segment posterior wall placenta

L - lower pole anterior wall placenta

L' = louer pole posterior wall placenta

||||| = anterior wall placenta

= posterior wall placenta

h = high venous drainage

? = no visible vessels

O = one side (right or left) venous drainage

V = various directions venous drainage

d = down: low venous drainage

Fig. 3.—The influence of the height of placental implantation upon uterine vascular pattern. Number of cases of certain drainage direction in each category of placental site.

veins (Fig. 3, LL'). The characteristic picture of prominent venous sinuses over the lower uterine segment in placenta previa is well known to every experienced obstetrician.

The vascular pattern of the mid-zonal placenta was of an intermediate type between the high drainage of the upper pole position and the low drainage of placenta previa. While some tendency to high drainage from the mid anterior wall of the uterus was still observed (Fig. 3, M), the drainage from the same region on the posterior wall (M') was almost evenly distributed in all directions.

The Effect of Parity on Uteroplacental Drainage.—It was noted during these observations that although the height of the placental site is the most

important factor determining the direction of drainage of the uteroplacental circulation it is by no means the only one. There are several other factors influencing the direction, the most essential of these being parity.

The placental positions and uterine vascular patterns in primigravidas were compared with those of multiparas (Fig. 4). A far greater frequency of high drainage of the uteroplacental circulation was a characteristic feature in primigravidas. It was observed not only from high-seated placentas but also from mid-zonal or even from low placentas seated on the anterior uterine wall. An exclusively lower drainage was found in primigravidas only in posterior wall lower pole placentas (Fig. 4, L').

			UC	) U' (")	M (	M' ( )	L	L'	
•	h	63	13	4	4	4	0	0	25
20011	?	0	1	0	0	6	1	1	9
igra	0	500	1	0	0	2	0	0	3
Frimigravidae	v	X	0	0	2	5	2	0	9
	d	R	0	. 0	0	0	0	5	5
			15	+ 4 - 19	6	+ 17 -23	3 +	6 = 9	51
	h	44	11	4	2	0	0	0	17
	?	0	0	0	1	6	0	2	9
9	0	Da	0	1	5	5	1	1	13
para	V	23	5	0	5	8	0	8	26
Multiparae	ď	R	0	0	J	6	4	9	22
-			16	+ 5=24	16	+ 25 - 41	5 +	20-25	87
			31	+ 9-40	22	+ 42 - 64	8 +	26 - 34	138

Fig. 4.—The influence of parity upon the drainage direction of the uteroplacental circulation. Primigravidas, upper part, multiparas, lower part.

In multiparas there was, on the contrary, a tendency to downward drainage not only in the low segment placentas but in the mid-zonal group as well, especially from the posterior wall. The upper pole placentas in multiparas have shown a drainage direction upward but with a far greater tendency to coexistent lower drainage than might be seen in primigravidas.

The entirely different vascular pattern in placenta previa and in high-seated placenta both in primigravidas and in multiparas suggests that a polar placental position plays the major role in determining the drainage direction. The development of uteroplacental circulation in the upper pole of the uterus with high-seated placenta determines its drainage through the higher circulation routes, whereas its development in the lower uterine pole makes the drainage downward predominant. Upper pole placenta is relatively more

frequent in primigravidas, lower pole placenta is far more frequent in multiparas. There is a general tendency to upward drainage in primiparas and to downward drainage in multiparas.

Uteroplacental Drainage in Toxemia and in Placenta Previa.—In view of the observed correlation between the placental site, drainage direction, and the appearance of toxemia or hemorrhage, it seemed interesting to compare the observations in pregnancies complicated by toxemia with those in placenta previa (Fig. 5). The tendency of patients with high-seated placentas to develop toxemia has been mentioned and may well be seen here with 24 upper segment placentas in 31 cases of toxemia. The uterine venous pattern has shown a predominance of the higher circulation vessels in toxemia with an exclusively high drainage in 21, and combined high and low drainage in 4 additional cases. In the remaining 6 there were no visible vessels at all. There was not a single case of exclusively lower drainage of the uteroplacental circulation in this group.

PREECLAMPSIA - ECLAMPSIA

PLACENTA PRAEVIA

		U	U' (^)	M (m)	M' ()	L Q	r. 🕙	Total	Total	L @	r 🕙
h	64	45	4	0	2	0	0	21	0	0	0
?	0	1	1	1	3	0	0	6	4	1	3
0	203	1	1	0	1	0	0	3	2	1	1
v	2	1	0	0	0	0	0	1	10	2	. 8
d	Ω	0	0	0	0	0	0	0	18	4	14
		18	+ 6-24	1	+ 6 - 7	0	0	31	34	8	26

Fig. 5.—Placental position and uterine drainage pattern in pre-eclampsia-eclampsia and placenta previa. Note reversed frequency of uterine drainage direction in pre-eclampsia-eclampsia and placenta previa seen in the two columns designated "total."

In placenta previa there was quite the opposite venous pattern with marked prominence of the veins of the lower circulation. They were visible as the only vessels in 18 cases of placenta previa and the predominant vessels in 12 others, where some veins of the upper circulation were visible simultaneously. There was not one case in this group where the vessels of the upper circulation route alone were prominent, the vessels being not visible at all in the remaining 4 cases (shock after massive hemorrhage). The contrast in blood drainage direction in toxemia and placenta previa is well seen in Fig. 5, particularly with the columns of totals.

Most surprising were the observations in 3 cases of eclampsia in which there were no vessels visible at all. It might be tentatively explained by the sudden change from hydremia and hypervolemia with increased salt and water retention and overfilling of the intravascular compartment, characteristic of pre-eclampsia, to hemoconcentration and hypovolemia associated with imminent eclampsia. The same phenomenon of disappearance of blood vessels in imminent eclampsia was observed by Hinselmann<sup>21, 22</sup> on the capillary part of the vascular system.

## Comments

The results presented and shown in Table I and Fig. 2 suggest that there is a correlation between the height of the placental site and the severity of toxemic or hemorrhagic complications. A tendency to higher placental location within the uterine cavity was marked in toxemia, to the mid-zonal position in normal pregnancies and in abruptio placentae with signs of both toxemia and hemorrhage. Pregnancies complicated by other types of bleeding had usually a low placental position. The correlation between the height of the placental site and the severity of complications, toxemic or hemorrhagic, is best to be seen in Fig. 2 showing placental positions in different groups of pregnancy, normal or complicated. The blood pressure falls from the most severe forms of toxemia with usually the highest placental site within the uterine cavity to the milder forms, with the lowest values in the placental previa groups.

The two basic questions put forward earlier, whether the placenta is really implanted at a high level in toxemia, and whether there are really different directions of drainage from a high-seated placenta in contrast to placenta previa may be affirmed already with some confidence. It can be concluded in general that a high-seated placenta and an upward drainage through the pampiniform plexuses and ovarian veins was most frequently found in pre-eclampsia-eclampsia, whereas a discharge of the uteroplacental blood downward through the uterine and hypogastric veins was, on the contrary, characteristic of placenta previa.

There are, however, important exceptions to this rule with occasionally even toxemic signs in a case of placenta previa (3 in 44 cases = 6.8 per cent) or a fundal placenta in a normal pregnancy (3 in 58 cases = 5.2 per cent).

Comparing these figures with the 70 per cent frequency of upper segment placentas in the toxemia group and 22.4 per cent in the normal pregnancy group we see that such coincidence is far less frequent than might be expected on the assumption that there is no correlation at all between placental site, toxemia, and/or hemorrhage. In all these cases the drainage of blood of the uteroplacental circulation was atypical being predominantly low from a highseated placenta in 3 multiparas who showed no pre-eclampsia-eclampsia, and predominantly high in 2 of the 3 primiparas who did show symptoms of preeclampsia-eclampsia with placenta previa. Our interpretation of these findings is that a predominantly high drainage of the uteroplacental circulation with a discharge of large blood masses toward important visceral organs and with the ensuing hemodynamic and metabolic disturbances, is probably the most important factor in promoting the pre-eclampsia-eclampsia syndrome. The placental position as the center of uteroplacental circulation is a very important factor in determining the direction of blood discharge. There are, however, many other important factors which may modify the correlation between the placental position and pre-eclampsia-eclampsia. The role of parity was mentioned; there are several other factors which may influence the drainage direction of the uteroplacental circulation in one way or another and which must be studied in a greater amount of material than it is possible to obtain in a short time among cases of cesarean section. The correlation of the placental site and toxemic or hemorrhagic complications of pregnancy will therefore be examined on the basis of a far greater material obtained through x-ray placentography studies (Part III). The anatomic conditions for a possible blood discharge from the uteroplacental circulation (Part IV) as well as functional and metabolic effects upon the pregnant organism (Part V) will be related in further communications.

The importance of vascular adaptations to the changes of pregnancy was not duly estimated by most writers on the subject, only few studies having been made on the blood flow from the uterus at different periods of pregnancy. Barcroft and co-workers4, 5 have found an important feature of the gross vascular relations of the uterus in numerous anastomoses particularly in the venous network. This serves the purpose of preventing hemostasis in the event of occlusion of any part of the venous system and thus preventing intrauterine bleeding. These authors noticed that the greatly enlarged anastomosing veins which receive the blood returning from the placental lake have an aggregate diameter larger than that of the veins into which they empty.

Reynolds, 36-39, 41 Reynolds and Gillespie, 40 and Gillespie, Ramsey, and Reynolds, 19 who made extensive studies on uterine hemodynamics during pregnancy in experimental animals stated: "Despite the fact that unusual adjustments are necessary in the circulatory system during pregnancy the nature and extent of these have been studied relatively little. Progress in this direction has not been in proportion to the importance of the problem." Extensive and progressive readjustment is necessary in the hemodynamics of the circulation as pregnancy advances and new pressure relationships develop within and about the circulatory system. The flow of maternal blood is affected in uterine veins, diminishing as the tension in the tissue increases while the conceptus is spheroidal. With the decrease in tension in different parts of the uterus, when the conceptus in the rabbit changes to a cylinder on the twenty-second day of pregnancy, the rate of maternal blood flow is restored proportionately.

Sampson44 called the uterus a "muscular venous sponge" to emphasize the extensive venous development within the uterus. Kearns<sup>27</sup> found in women at 7 months an increase in the number of sinuses below the placental site and a decrease in the number of vessels on the placenta-free side of the

uterus over that of the 2 months' gestation.

McRoberts<sup>30</sup> and Howard, Goodson, and Mengert<sup>26</sup> found that compression of the inferior vena cava by the flaccid uterus near term may cause a hypotension syndrome which they explain on the basis of blood engorgement within the pelvis and lower extremities. Mengert and his associates<sup>31</sup> came further to the conclusion that this phenomenon may be important in the pathogenesis of premature separation of the normally implanted placenta. He produced abruptio placentae in 2 women during the course of cesarean

hysterectomy by simple compression of the vena cava.

Venous pressure studies performed on women during pregnancy have been largely confined to the study of the veins of the extremities. Runge, 43 Burwell, 12 Burwell and associates, 13 Albers, 1 and McLennan 29 all found a progressive increase in venous pressure especially in the lower extremities. In animal experiments Burwell and his co-workers<sup>13</sup> found that the venous pressure increased as the point of measurement approached the placenta. Bickers<sup>10</sup> indicated a relationship between the location of the placenta to the left or to the right and elevated venous pressures on the left or the right

extremity.

Hodgkinson,24,25 and Hodgkinson and Christensen23 stated that little is known of the manner in which the vascular system compensates for the demands of pregnancy. The magnitude of the development of the veins in relation to the pregnant uterus is not generally appreciated. From comparative measurements of the diameter of the ovarian vascular pedicle in the nonpregnant and the pregnant woman, Hodgkinson found that the capacity of these veins increased over sixty times by the thirty-sixth week of pregnancy and the tension of their wall increased over two and one-half times. The blood of the pelvic venous system is in a state of dynamic physiologic activity and there is an increased workload imposed during pregnancy, which is unparalleled in human vein physiology.

Rosenfeld and Lapan<sup>42</sup> reported an average venous pressure of 180 mm. of water in uterine sinuses during pregnancy. Hellman and co-workers20 found during cesarean sections pressures of 120-600 mm. of water in the amniotic fluid and 140-510 mm. of water in the intervillous space. Alvarez and Caldeyro-Barcia<sup>2, 14</sup> and Caldeyro-Barcia<sup>15</sup> stated that each uterine contraction exerts approximately 3 times as much pressure on the intramyometrial vein than on the amniotic fluid cavity. A contraction increasing the amniotic pressure to 40 mm. Hg exerted a pressure of 120 mm. Hg on the intramyometrial vein. The flow of maternal blood through the placenta is a function of the difference between the mean arterial pressure and the intramyometrial pressure. The mean arterial pressure of the mother is the effective pressure forcing the blood through; myometrial pressure is the most important resistance to the blood flow. At the acme of the contractions when it is the highest, the blood flow through the uterus and placenta is completely arrested for a brief period. Wright and her co-workers46 suggest a concept of an intermittent nature of the blood flow through the uterine muscle during labor. They assume that it behaves in a way similar to skeletal muscle and that a compensatory hyperemic phase follows a contraction.

It is obvious that although the blood may be interrupted at the height of a uterine contraction the discharge into the draining venous system must be even more forceful and impetuous after the release of the uterine contraction. If the enormously increased blood mass carried through the uteroplacental circulation in advanced pregnancy is discharged predominantly in one direction, either up or down, there is with the new redistribution of blood mass and the following obstruction of blood flow the possibility of multiple and manifold toxemic complications or hemorrhages depending on where the disturbance is most evident.<sup>6, 7, 9</sup> With the predominant drainage upward through the ovarian veins it might be the kidneys, or by way of segmental communications and the extensive venous vertebral system, the brain; with a direction through the developing portosystemic anastomoses it might be the liver. The predominance of symptoms from the most disturbed organ might cause either a renal, or a liver, or a cerebral form of pre-eclampsia-eclampsia.45 In case of predominant drainage down toward a congested pelvic vasculature different forms of obstetrical hemorrhage might be produced. 6-9 If, on the other hand, the pregnant uterus is drained through all possible channels, through both uterine and both ovarian plexuses, to a varying degree up and down and to the left and to the right, the strong uteroplacental circulation is divided into several small, weak streams which do not materially disturb the hemodynamics in either direction, securing a progress of physiologic pregnancy without complications. Guilhem and Baux<sup>18</sup> have thoroughly studied the venous drainage of the pelvis and have discerned the individuality of all those currents, the parietal and the visceral ones, the right and the left routes; unfortunately, there is very little known about such conditions during preg-

The basic importance of all these facts pertaining to the physiology and pathology of uterine hemodynamics, especially in its highly disregarded venous part, and its influence upon the whole organism cannot be overemphasized. The veins are not the passive, lifeless vessels they were commonly stated to be half a century ago, but in many instances extremely reactive tubes, often much more so than the corresponding arteries.<sup>17</sup> It is our purpose to show further how the uteroplacental circulation may initiate complications

of pregnancy, toxemia, or hemorrhage as a result of its predominantly high or low venous discharge. The drainage of the pregnant uterus might thus be one of the fundamental problems of obstetric pathology.

#### Conclusions

1. Observations during 183 cesarean sections have shown a significantly greater frequency of high-seated (fundal and upper segment) placentas in pre-eclampsia-eclampsia as compared to normal pregnancy in which the mid-segment placenta was most frequent. In hemorrhage complicating pregnancy a low-seated placenta prevailed; only abruptio placentae with both toxemia and hemorrhage has usually shown a mid-zonal placental position.

2. There was, to a certain extent, a correlation between the height of placental site and the prominence of toxemic signs on the one hand; between the low level of placenta and the severity of hemorrhage on the other.

3. There were entirely different vascular patterns of the pregnant uterus suggesting an upward drainage of the uteroplacental circulation through the ovarian veins in high-seated placenta and a downward drainage through the uterine veins in placenta previa.

4. The drainage of the pregnant uterus was influenced by other factors beside the placental site; among these parity was the most important. The vascular patterns have shown a marked trend to high drainage in primigravidas, contrasting with a tendency to low drainage or a discharge in various directions in multiparas.

5. A tendency to high drainage may be observed in pregnancies complicated by pre-eclampsia-eclampsia, contrasting with low drainage in placenta previa.

6. The development of an extensive uteroplacental circulation in advanced pregnancy and its predominant drainage in one direction may be a causative factor in the development of toxemia or hemorrhage. The drainage of the pregnant uterus and its effects on hemodynamics and metabolism of the pregnant woman are problems of basic importance in obstetrical pathology.

# Summary

The observations presented support the author's hypothesis that drainage of the uteroplacental circulation predominantly in one direction, up or down, might cause a pathologic redistribution of blood with hemodynamic and functional disturbances: toxemia in high drainage toward the kidneys and visceral circulation, and hemorrhage in predominant low drainage and engorgement of blood in the pelvic vasculature.

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- 3, 1958.

# HYPERTENSIVE LINEAGE AND TOXEMIA OF PREGNANCY\*

 $\mathbf{Michitaka}$  Kaku, M.D., and Hidekazu Nagata, M.D., Kumamoto, Japan

(From the Department of Obstetrics and Gynecology, Kumamoto University School of Medicine)

FOR years, investigators have been interested in the theory that toxemia is of constitutional origin. Recent studies of this view have been accelerated by the proposal of an allergic basis for this condition.

It has been demonstrated clinically that the patient with essential hypertension is more apt to develop toxemia of pregnancy. This fact has been confirmed in experimental animals also.<sup>16</sup> Moreover, most investigators of the present day emphasize the hereditary nature of essential hypertension. For this reason we have studied the relationship between hypertensive lineage and toxemia of pregnancy, in an effort to clarify the etiology and to improve the prophylaxis of this disease syndrome.

#### Method

We checked the blood pressure of every available relative of the hypertensive patients who visited either our department or the department of Diathetic Medicine, Kumamoto University School of Medicine.

The definite hypertensive lineages were thus selected. Then the past histories, including previous gravidity of multiparas in these families, were investigated. If the relatives were found to live in outlying areas, we either contacted them by mail, soliciting medical data, or investigated them through their own local physicians. Those who had died were also included if the history was definite and reliable.

As defined by the Department of Diathetic Medicine, hypertension is a systolic pressure over 130 mm. Hg in the age group under 19 years, over 140 mm. Hg in the group between 20 and 39 years, over 150 mm. Hg in the fourth decade, and over 160 mm. Hg in the group over 50 years. Diastolic is 80 mm. Hg under 19, 90 mm. Hg for men and 85 mm. Hg for women in the second decade, 90 mm. Hg in the third, 95 mm. Hg in the fourth, and 100 mm. Hg for men and 95 mm. Hg for women over 50 years old.

So-called apoplexy is a term indicating not only a cerebrovascular hemorrhage but also either embolism or thrombosis, so that it is not caused by hypertension alone. It is clinically evident, however, that in the majority of cases of apoplexy there is a history of hypertension. Previous studies<sup>1, 2, 3</sup> revealed that a history of hypertension is found in 90 per cent or more of all cases of apoplexy. The Department of Diathetic Medicine<sup>4</sup> also studied each death in Kumamoto districts, which was thought to have been associated with

<sup>\*</sup>Presented at the seventh meeting of the Japanese Constitutional Medical Association and the ninth meeting of the Japanese Obstetrical and Gynecological Society.

an attack of apoplexy or hemiplegia. The incidence of hypertension was 96 per cent. It therefore seems fair to assume, for all practical purposes, that apoplexy indicates an associated hypertensive state.

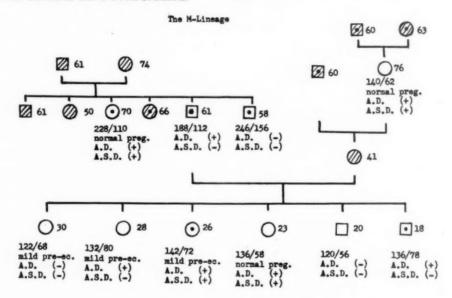
These authors selected bronchial asthma, urticaria, and drug allergy as allergic manifestations, and migraine as evidence of angiospasm (on the basis

of the reports of various authorities. 5-9).

As to the patients delivered at home, those with marked edema of both legs or the entire body were considered to have had toxemia of pregnancy.

# Results

To date, 54 families with hypertensive lineages and 164 multiparas in their families have been studied.



A.D.: Allergic Diathesis

A.S.D.: Angiospastic Diathesis

Fig. 1.

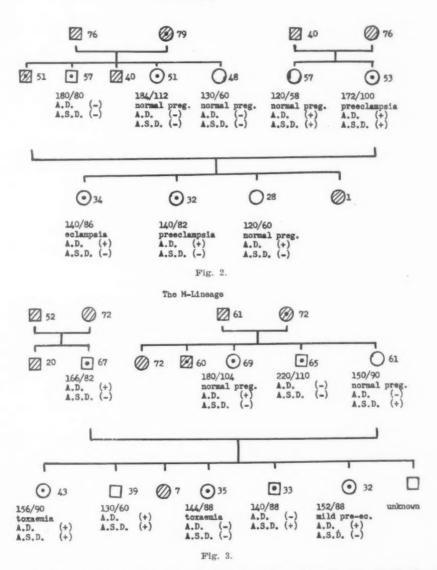
Three cases of hypertensive lineage are presented in Figs. 1 to 3. In these illustrations, a male is indicated by a square mark and a female by a circle. Oblique lines indicate those who have died and a dot indicates a person with evidence of definite hypertension and/or apoplexy in his history. The numbers at the right of the symbols show the ages of the individuals at the time of this study or at the time of death. The horizontal ranking of brothers and sisters was ordered from left to right.

1. Toxemia of pregnancy occurred in 56, or 34 per cent, of 164 multiparas. Among the controls, however, the disease was recognized in only 12 of 147 multiparas (8 per cent). The controls were selected at random from patients with nonhypertensive lineages. The incidence is obviously higher in the hypertensive lineages. From the view of inductive analysis by Yate's modification of the chi-square test, the level of significance was under 0.5 per cent, which indicates a highly significant difference.

2. The relationship between the allergic diathesis and toxemia of pregnancy was studied in 157 multiparas in the hypertensive lineages whose past

histories were available in detail. Toxemia occurred in 32 of 58 patients, or 55 per cent, with allergic diathesis and in 22 of 99 in the nonallergic group, or 22 per cent. Apparently the incidence is higher in the allergic group. From the view of inductive analysis, the level of significance was under 0.5 per cent, which indicates a highly significant difference.

#### The U-Lineage



A similar study on the relationship between the allergic diathesis and toxemia of pregnancy was performed in patients with nonhypertensive lineages. In this study, the incidence of toxemia was 7 of 43 cases, or 16 per cent, with the allergic diathesis; that of the nonallergic was 5 of 104 cases, or 5 per cent. This is also statistically significant.

3. As to the angiospastic diathesis and toxemia of pregnancy in hypertensive lineages, the incidence was 48 per cent (24 of 50 cases) among the patients with the angiospastic diathesis, and 28 per cent (30 of 107 cases) of those without it. From the view of inductive analysis the level of significance was under 2.5 per cent which indicates a significant difference. This result also confirms the fact that the incidence is high in the angiospastic group.

In the nonhypertensive lineages, the incidence of toxemia was 29 per cent (5 of 17 cases) among patients with the angiospastic diathesis and 5 per cent (7 of 130 cases) of those without it. Apparently this is high in the angiospastic cases and the level of significance was under 0.5 per cent.

4. The allergic diathesis of multiparas in hypertensive and nonhypertensive lineages was studied. It was found that 58 out of 157 patients with hypertensive lineages (37 per cent) had allergies. In nonhypertensive lineages the incidence was 43 of 147 cases (29 per cent). The former is slightly higher than the latter but the difference is not significant statistically.

A similar study on the diathesis of angiospasm was performed. Here 50 of 157 patients, or 32 per cent of those with hypertensive lineages and 17 of 147 or 12 per cent of those with nonhypertensive lineages showed evidence of the angiospastic diathesis. From the view of inductive statistics, the level of significance was under 0.5 per cent which indicates a highly significant difference.

#### Comment

The etiology of toxemia of pregnancy is still unknown. It is generally recognized, however, that the disease is seen often in members of the same family. Syozi¹⁰ and Bassett¹¹ have referred to such a correlation in their reports. Therefore there remains little doubt that heredity plays an important role in the etiology of toxemia. It is more reasonable, however, to consider that the original predisposition to manifest the disease may be inherited. Therefore, the intensive study of the predisposition as mentioned in the introduction becomes quite important.

Seitz<sup>12</sup> and others<sup>13-15</sup> have reported that there is clinical evidence of a high incidence of toxemia among patients with essential hypertension. Ban,<sup>16</sup> one of our associates, demonstrated that hypertensive rabbits showed eclampsia-like changes in their important organs more markedly than non-hypertensive rabbits. Furthermore, the majority of authorities<sup>1, 17-19</sup> has recognized the fact that there is a hereditary aspect to hypertension and, therefore, it may be presumed that a predisposition to hypertension is an important element in the constitutional background of toxemia. The incidences of toxemia of pregnancy as reported by different authorities do not coincide with each other, but the average figure is approximately 10 per cent (Table I). After their analysis of the hypertensive lineages, the authors listed have concluded that a hypertensive family background predisposes the patient to toxemia of pregnancy.

Recently, the allergic theory of toxemia has been supported by many authorities, 20-26 and it is considered that this allergic tendency is an etiological factor in this disease. There are also many reports on this subject. 7, 10, 26-28 Our associate, Yunohara, 26 performed experimental studies on the vaccines of typhoid fever and emphasized that many toxemia patients have an allergic predisposition and that the ability to produce an antibody easily in vivo is likely to be associated with a tendency toward toxemia. In this study we also found that many women with a predisposition to hypertension, especially allergic types, have the tendency to suffer from toxemia of pregnancy more frequently, even when they are not actually hypertensive.

TABLE I. THE INCIDENCE OF TOXEMIA

REPORTER	INCIDENCE (%)	
Kushima <sup>29</sup>	18	
Yashiro <sup>30</sup>	13	
Gemmel <sup>31</sup> (primiparas)	9.8	
Burt32	8.2	
Nakatu <sup>33</sup>	7.96	
Kaku <sup>34</sup>	7.16	
Gemmel <sup>31</sup> (multiparas)	7.0	
Hozaki <sup>35</sup>	6.3	
Sawazaki <sup>36</sup>	5.6	
$Y_{0}g_{0}$ 37	4,56	
Eufinger <sup>38</sup>	4-5	
Obata <sup>39</sup>	3.06	

The primary cause of hypertension at the initial stage has been considered to be a spasm of the arterioles. Miyao18 and Maruyama6 reported that in hypertensive individuals angiospasm was found not only at the initial stage of the disease but also in the latent stage. Migraine is thought to be associated with peripheral angiospasm, which is not only localized in the brain but also generalized in other parts of the body. Though it is not considered to be the essential etiological factor, spasm in the arterioles, especially the blood vessels of the kidney, is an important pathological finding in toxemia. Therefore, the angiospastic factor is considered to be important as well as an allergic predisposition. In fact, our result showed that in both hypertensive and nonhypertensive individuals, women with an angiospastic tendency are apt to develop the disease.

# Summary

- 1. The incidence of toxemia in hypertensive lineages was 34 per cent, and that in nonhypertensive lineages was 8 per cent.
- 2. In hypertensive lineages, the incidence of toxemia is higher in patients with an allergic diathesis than in others. In nonhypertensive lineages, the incidence of toxemia was also higher in those with the allergic diathesis.
- 3. It was also found that the incidence of toxemia showed a significant difference in patients with angiospasm.
- 4. The allergic diathesis of multiparas in hypertensive and nonhypertensive lineages was reviewed and found to be more common in association with hypertension.
- 5. A similar study on the angiospastic diathesis was carried out, revealing a high incidence of this type of diathesis in hypertensive lineages.

Patients with the hypertensive diathesis tend to develop toxemia of pregnancy, together with either an allergic or an angiospastic diathesis. For this reason, the obstetrician should investigate these tendencies in each pregnant woman in order to discover susceptible subjects and protect them from the disease.

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# THE USE OF ANILERIDINE IN LABOR FOR THE CONTROL OF PAIN\*

M. J. Wizenberg, M.D., I. A. Siegel, M.D., W. Korman, M.D., and H. N. Rosenthal, M.D., Baltimore, Md.

(From the Department of Obstetrics, Sinai Hospital of Baltimore)

ANILERIDINE is an analgesic agent chemically related to meperidine, in which the N-methyl group of meperidine is replaced by N-(p-aminophenethyl). The full chemical name for anileridine is ethyl 1-(4-aminophenethyl)-4-phenylisonipecotate dihydrochloride. The empirical formula is  $C_{22}H_{28}O_2N_2$ · 2HCl (Fig. 1).

$$\begin{array}{c|c} COOC_2H_5 \\ \hline \\ N \\ CH_2 \\ \hline \\ CH_2 \\ \hline \\ NH_2 \\ \hline \\ Anileridine \\ \end{array} \begin{array}{c} COOC_2H_5 \\ \hline \\ CH_3 \\ \hline \\ \end{array}$$

Fig. 1.

# Pharmacology

Animal studies<sup>5</sup> have demonstrated excellent analgesic potency when anileridine is administered either subcutaneously or orally. In rats, anileridine administered subcutaneously is as potent as morphine and about twelve times as potent as meperidine; given orally in doses of 12 mg. per kilogram of body

<sup>\*</sup>This study was in part supported by a grant from Merck Sharpe & Dohme, Inc., who supply anileridine commercially under the name, Leritine.

weight or higher, the drug is as effective as when given subcutaneously. Maximal analgesia occurs in 20 to 30 minutes and lasts 4 to 6 hours with doses of 4 to 6 mg. per kilogram. Similar results are obtained in dogs.

The effect on respiration has been studied in cats and dogs anesthetized with pentobarbital. Morphine produces a more profound respiratory depression of longer duration than equal amounts of anileridine. The effect of anileridine and meperidine in equal doses (milligram for milligram) is not significantly different. (Note, however, that on a milligram-for-milligram basis, anileridine is a much more potent analgesic.) Intravenous administration of anileridine in doses of 2 mg. per kilogram to similarly anesthetized animals produces a gradual fall in blood pressure (a decrease of about 30 mm. of mercury in both species) lasting 30 to 60 minutes, with a mild bradycardia, the decrease in heart rate being 25 per cent or less. No significant changes in blood pressure are obtained with doses of up to 1.0 mg. per kilogram. Meperidine produces a slightly stronger effect and morphine a much more pronounced one, in equal doses.

No chronic toxicity has been observed in rats and dogs. The acute toxicity of anileridine in comparison with the effective analgesic dose indicates a high margin of safety. In rats, tolerance to the analgesic effect of anileridine is developed more slowly and to a lesser degree than to morphine or meperidine. The analgesic effects and side reactions of anileridine are antagonized by N-allylnormorphine in rats, cats, and dogs.

Studies carried out with human subjects<sup>4</sup> demonstrate an analgesic potency two and one-half times that of meperidine given intramuscularly. When given in equivalent analgesic doses the side effects are similar, with the exception that anileridine produces less sedation and is slightly shorter acting than meperidine. The onset of action is rapid and the analgesic effect in the immediate postoperative period lasts about 50 minutes following intramuscular injection, or 20 to 25 minutes after intravenous injection.<sup>2</sup> The injection of 10 to 25 mg. intravenously during general or spinal anesthesia produced respiratory depression, and apnea in 4 of 80 cases studied by Dripps<sup>2</sup>; the duration of this effect is shorter than with morphine or meperidine. (Note dosage scale for this study.) Hypotension is relatively uncommon.

Because of the previously described pharmacological features, an evaluation of the usefulness of this drug as an analgesic agent in the conduct of labor was undertaken.

#### Methods

Data used in this study were obtained from 155 service patients admitted to the delivery suite in labor. All patients who received anileridine prior to delivery were included in the series and a check sheet was used on which the following information was noted: complications in prenatal course, respiration, blood pressure, degree of sedation, time between last dose of drug and delivery, length of first and second stages of labor, type of delivery, birth weight of infant, degree of amnesia, and patient's subjective satisfaction. The condition of the infant at birth was evaluated by the method of Apgar¹ (Table I)

The patients were divided on the basis of parity into two groups (primigravidas and multigravidas) and each group was further divided on the basis of anesthesia used at the time of delivery, and whether the anileridine was used alone or in combination with barbiturates. All patients received 0.4 or 0.6 mg. of scopolamine with each initial dose of anileridine (Table II).

The initial studies evaluated oral, intramuscular, and intravenous administration, using varying doses. It was found that the most satisfactory

route of administration was intravenous injection. The usual dose of anileridine was 50 mg. together with 0.4 or 0.6 mg. of scopolamine. This was repeated as necessary after an interval of one hour or longer. Some patients received amounts slightly larger or smaller than the usual 50 mg. dose. In a few cases the anileridine was given intramuscularly either for the initial or repeat doses. The group which received barbiturates in addition were originally given 0.2 Gm. of secobarbital sodium by mouth or 100 mg. of pentobarbital sodium intravenously. These doses of barbiturates were halved early in the experiment when we found the degree of sedation produced was excessive. Used in this manner the combination of anileridine and a barbiturate proved quite satisfactory.

TABLE I. THE EVALUATION OF THE NEWBORN INFANT BY APGAR<sup>1</sup> METHOD OF SCORING\*

SIGN	0	1	2
Heart rate	Absent	Slow (below 100)	Over 100
Respiratory effort	Absent	Slow (irregular)	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink Extremities blue	Completely pink

<sup>\*</sup>Sixty seconds after the complete birth of the infant (disregarding the cord and placenta) the above five objective signs are evaluated and each given a score of 0, 1, or 2. A score of 10 indicates an infant in the best possible condition.

TABLE II. CLASSIFICATION OF PATIENTS IN STUDY

	PRIMIGRAVIDAS	MULTIGRAVIDAS	TOTAL
Anileridine.—			
+ General anesthetic	7	31	38
+ Conduction anesthetic	16	44	60
Anileridine + Barbiturate			
+ General anesthetic	9	13	22
+ Conduction anesthetic	14	21	22 35
Total	46	109	155

#### Results

The results were evaluated on both objective and subjective bases, and the maternal satisfaction with the analgesia and amnesia was evaluated post partum.

The drug proved to be very rapid in onset of action. In the cases where the anileridine was administered intravenously, there were almost immediate analgesia and sedation. Most patients promptly went to sleep and remained so for about one hour, and in some cases for as long as 2 hours or more. Beyond this time (one hour) supplementation was usually required. The patients were easily aroused, and, while some reacted with movement or moaning at the height of a uterine contraction, for the most part they rested quietly. In only 10 cases of 155 did the patients become excited and difficult to control; in one of these instances this occurred as the sedation was wearing off.

It was interesting to observe the rarity of side effects. Respiratory depression or alteration in blood pressure was not observed with the dosage

described. There was usually a tachycardia which we observed with or without the use of anileridine and which we attributed to the scopolamine. Nausea and vomiting during labor were extremely rare. Only one patient exhibited what might possibly be considered an allergic manifestation, although we cannot be sure that this was due to the anileridine. (The patient also received scopolamine, vitamin K, and oxytocin.) This patient noticed a fine macular rash on her arms 6 hours post partum. There was no itching and the rash disappeared spontaneously within a few hours.

The condition of the infant was evaluated at the time of delivery by the method previously described (Tables III and IV). The figures we present are uncorrected. The figures in Table V are arranged from the control group used in an experiment carried out in this institution on the obstetrical use of N-allylnormorphine. These cases are presented in an attempt to derive a comparison between anileridine and meperidine. Sedation was given to these control patients with meperidine, scopolamine, and usually secobarbital or pentobarbital. The majority of infants in the anileridine series with evaluations below 8 suffered from secondary apnea which responded rapidly to suction and oxygen by mask with or without the use of intermittent positive pressure. In only one case was N-allylnormorphine used; 0.2 mg. was given to the newborn with a prompt response.

TABLE III. EVALUATION OF INFANTS IN ENTIRE SERIES WITH REFERENCE TO PARITY, METHOD OF SEDATION, ANESTHESIA, AND DELIVERY

		PRIMIG	RAVIDAS			MULTIG	RAVIDAS	
	ANILEI	RIDINE	ANILERI BARBIT	URATE	ANILEI		ANILER	
	GENERAL ANES- THESIA	CON- DUCTION ANES- THESIA	GENERAL ANES- THESIA	CON- DUCTION ANES- THESIA	GENERAL ANES- THESIA	CON- DUCTION ANES- THESIA	GENERAL ANES- THESIA	CON- DUCTION ANES- THESIA
Number	7	16	9	14	31*	44	13	21
Spontaneous delivery Low forceps	1 6	$\begin{smallmatrix} 0\\16\end{smallmatrix}$	1 8	1 13	13 15	11 29	10	4 15
Midforceps Average Apgar	Ö	0	0	0	1†	4†	0	2†
evaluation; % cases with evaluation	7.1	8.6	8.0	8.6	7.4	9.0	7.2	8.1
< 8‡	43	13	33	14	32	14	46	29

The difference in Apgar evaluation for those receiving anileridine alone and those receiving it with barbiturate in any comparable group is not statistically significant.

\*Two breech extractions included in 31.

†All midforceps rotations were elective.

‡All figures uncorrected.

TABLE IV. EVALUATION OF INFANTS IN ENTIRE SERIES

All cases with anileridine alone	8.2
All cases with anileridine + barbiturate	8.0
All cases with general anesthesia	7.4
All cases with conduction anesthesia	8.65
Over-all average	8 9

The difference in evaluation obtained with anileridine and with anileridine plus a barbiturate is not statistically significant.

The results with anileridine and meperidine are compared in Table V. It is readily apparent that consistently better evaluations were obtained with anileridine than with meperidine.

TABLE V. COMPARATIVE EVALUATION OF INFANTS WITH ANILERIDINE AND MEPERIDINE<sup>6</sup>

		DINE +	BARBIT			RIDINE
	GENERAL ANES- THESIA	CON- DUCTION ANES- THESIA	GENERAL ANES- THESIA	CON- DUCTION ANES- THESIA	GENERAL ANES- THESIA	CON- DUCTION ANES- THESIA
Number of patients Average Apgar evaluation % with score < 8	19 7.2 47	39 7.7 33	22 7.5 41	35 8.5 23	38 7.3 34	60 8.9 13

The interval between the last dose of anileridine and delivery varied from 12 minutes to over 210 minutes. There was no significant relationship between this interval and the infant's condition at birth.

With the exception of 2 cases, all infants weighed in excess of 5 pounds, 9 ounces. The 2 small infants weighed 5 and 5½ pounds and received evaluations of 9 and 10, respectively. (It is the usual practice in our institution to use continuous caudal or epidural analgesia and anesthesia in cases of prematurity.)

On the day following delivery the patients were interviewed with regard to the degree of amnesia which had been obtained and the degree of satisfaction of the individual patient with the method used to provide analgesia. In a

few cases (7) no evaluation was recorded.

In interpreting the figures in Table VI it should be noted that 98 patients received no barbiturate. It is well known that the greatest degree of amnesia and subjective satisfaction is achieved by the combined use of narcotics, scopolamine, and one or more barbiturates, often in amounts sufficient to affect the infant.<sup>3</sup> We were able to obtain good-to-excellent amnesia in 64 to 66 per cent of mothers and subjective satisfaction with the method in 83 to 85 per cent of cases.

TABLE VI. SUBJECTIVE EVALUATION BY PATIENTS

	POOR	SATISFACTORY	EXCELLENT
Amnesia.—			
Anileridine alone (98 cases)	36%	17%	47%
Anileridine + barbiturate (49 cases)	24%	17%	59%
Subjective Satisfaction.—			
Anileridine alone (98 cases)	17%	25%	58%
Anileridine + barbiturate (49 cases)	15%	25%	60%

In the entire group studied there were no maternal or infant deaths. Two mothers had postpartum hemorrhages caused by relaxation of the uterus, and one had a mild degree of premature separation of the placenta late in labor. The length of labor was not affected by the use of anileridine.

#### Conclusions

- 1. Anileridine is a satisfactory drug for use as an analgesic in labor. Used in 50 mg. doses intravenously, it is rapid in onset of action, but shorter in duration than meperidine used in 100 mg. doses intravenously. No maternal respiratory or blood pressure depression is observed when used as described in our series.
- 2. The drug may be used in combination with barbiturates, but there appears to be some degree of synergism with marked sedation of the mother

and often of the infant if full doses of the barbiturate are used. We recommend not over 100 mg, of secobarbital by mouth or 50 mg, of pentobarbital intravenously.

- 3. The condition of the infant at the time of delivery evaluated by the Appar method is satisfactory and, when compared with a group sedated with meperidine (in the same hospital), shows a higher rating, although the latter is not statistically significant.
- 4. Better ratings are obtained by the use of conduction anesthesia than with general anesthesia.
- 5. In infants who are narcotized, secondary apnea seems to be the commonest problem and usually responds to simple therapy.
  - 6. A possible allergic reaction was observed in only one case.
- 7. Satisfactory-to-excellent analgesia was obtained in a high number of cases and 83 to 85 per cent of patients were satisfied with this drug used for relief of pain in labor.

We wish to acknowledge with thanks the assistance of Todd M. Frazier, Director of the Bureau of Biostatistics, Baltimore City Health Department, in carrying out the statistical evaluation of our results.

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# TERMINAL OBSTETRICAL ANESTHESIA BY MEANS OF LUMBAR SYMPATHETIC PARAVERTEBRAL BLOCK

JAMES M. RIEKSE, M.D., GRAND RAPIDS, MICH.

(From the Department of Obstetrics and Gynecology, Butterworth Hospital)

IN 1933 Cleland¹ demonstrated that the pain of labor could be abolished by paravertebral block of the eleventh and twelfth thoracic roots by local anesthetic agents. He used 5 c.c. of 1 per cent Novocain and epinephrine in the region of each nerve root bilaterally. At that time he reported 5 cases in which the labor was terminated with caudal anesthesia for the second stage of labor, since paravertebral blocks did not abolish the pain of this stage of labor.

In 1944, Jarvis<sup>2</sup> reported 70 cases in which paravertebral sympathetic block anesthesia was used for the pains of labor. He used a single injection of 30 c.c. of 1 per cent procaine on each side of the spine between the transverse processes of L-1 and L-2. These were repeated as necessary and the second stage was managed by the addition of a pudendal block for perineal anesthesia.

Reich,<sup>3</sup> in 1951, reported a series of 500 deliveries managed by a continuous paravertebral lumbar sympathetic block bilaterally. His method consisted of a single needle insertion on each side between L-1 and L-2, injecting 25 c.c. of 1 per cent procaine on each side and then threading fine vinyl plastic tubing through the needles and removing the needles. Additional procaine was injected through the tubing as needed. The second stage was managed by doing a pudendal block.

In 1953, a number of obstetricians on the staff of Butterworth Hospital, stimulated by Reich's report, began using paravertebral lumbar sympathetic block anesthesia on selected patients in labor. The various ramifications of the method were explored and progressive development of the method occurred in collaboration with Dr. Mary Lou Byrd, chief of anesthesia of Butterworth Hospital. In all, some 2,500 patients have been given this type of anesthesia in various combinations with several different anesthetic agents.

Inadvertently, it was discovered that some patients came to the delivery room with complete perineal anesthesia and delivered painlessly without additional anesthesia. These were not the result of errors in technique with subsequent subarachnoid injection, since the effect was bilateral and symmetrical, and, if given into the spinal canal, the amount of material injected would have been catastrophic. It was noted that this phenomenon occurred in those

patients in which the blocks were given while they were in labor beds, and that the back rests of the beds had been elevated during the remainder of the labor. It was then found that this effect could be duplicated in the delivery room and thus used as terminal anesthesia.

#### **Procedure**

In primigravidas the procedure is instituted at 8 cm. dilatation, and in multiparas at 6 to 8 cm. The head should be down well in the pelvis, and the preceding labor should have been well developed. The patient sits on the edge of the delivery table with her feet on a chair. She is supported by an attendant and the neck and back are flexed as in doing spinal blocks. The iliac crests on each side are palpated to locate the level of L-4, and the spinous processes of either L-3 or L-2 are located as points of reference. The skin of the back is then prepared and the procedure performed with sterile technique. Using 1 per cent Xylocaine, skin wheals are made 4 cm. laterally to the superior point of the spinous process of either L-2 or L-3 on each side and the subcutaneous tissues infiltrated with 2 c.c. A No. 2 nerve block needle is inserted at right angles and advanced to the transverse process of the vertebra. This will be struck within 2 to 4 cm, thus giving another point of reference. The needle is then withdrawn slightly and inserted just beneath the transverse process and angled approximately 30 degrees toward the midline and advanced until it comes in contact with the vertebral body. This again is a definite endpoint, since a very distinct grating sensation is felt when the vertebral body is reached. The needle is now withdrawn slightly to avoid subperiosteal injection. By this time the needle is usually inserted to a depth of approximately 4 to 6 cm. Aspiration with an empty syringe in 360 degrees is now done to determine the absence of blood or spinal fluid. Sixteen c.c. of 1 per cent Xylocaine is then injected at a moderately slow rate without undue pressure with a Luer-Lok syringe. The procedure is repeated in the same manner on the opposite side and the patient immediately placed on her back on the delivery table. The table is now cranked to elevate the head of the table and depress the feet to an angle of approximately 20 degrees.

Upon completion of the procedure, the pain of the uterine contractions is usually immediately abolished. The perineal anesthesia is now awaited. This develops slowly, reaching its full effect in 15 to 20 minutes. During this time the blood pressure is recorded every 2 or 3 minutes and vital signs are carefully watched. When the anesthesia is fully established, the sensory level is usually found to be at the level of the umbilicus. There is either marked weakness of the legs or motor anesthesia. The involuntary bearing down reflex is lost, but the voluntary abdominal effect is retained, although it may be mildly impaired. Rectal and perineal tone are completely abolished.

The uterine contractions continue and the membranes are ruptured at this point if still intact. The delivery is then conducted as under caudal or spinal anesthesia.

#### **Technical Considerations**

This procedure is remarkably simple to perform. The time required and the technical proficiency required are similar to those required for a pudendal block. It also bypasses some of the inherent dangers associated with spinal and caudal anesthesia and shares the advantages to the fetus and mother of local and regional anesthesia. In spite of its technical simplicity, certain precautions are necessary and a number of complications may occur. Among the complications are: (1) inadvertent subarachnoid injection, (2) intravascular

injection, (3) drug reactions to the agent used, and (4) hypotension. The first two can be avoided by proper and careful technique. Individuals who are sensitive to local anesthetic agents should be screened out by history and the total number of reactions kept to a minimum by using an agent such as Xylocaine, which causes few side reactions.

Approximately 20 per cent of our selected patients develop some significant hypotension. This ordinarily develops within the first 10 minutes of the anesthesia and is usually heralded by nausea and retching. If no hypotension occurs in the first 10 minutes, it probably will not occur. The hypotension is easily controlled in most cases by putting the patient's legs up in stirrups and maintaining the tilt of the table. Since delivery usually occurs within an hour after administration of the anesthetic, the patient may be kept in this position until after delivery without too much inconvenience. The most physiological method of restoring normal blood pressure is to turn the patient on her side. Intramuscular or intravenous ephedrine may also be used in more severe cases. These methods, as a rule, promptly return the levels to normal and the blood pressure stabilizes after 15 minutes. Oxygen administration by mask is given to the mother to protect the fetus if the pressure drops below 80 systolic. This is usually a transient episode, but must be watched for carefully.

In some patients, especially those with occipitoposterior positions, the driving force of the labor seems to be lost and a persistent rim of cervix remains until it is lifted over the presenting part. This is easily done since the cervix is paralyzed, soft, and without tension. Voluntary efforts on the part of the patient then complete the labor. On occasion this has been obviated by the use of a dilute intravenous Pitocin drip.

#### Selection of Patients

As previously mentioned, this technique, by trial and error, has been found to be most successful in those patients whose labor has been normal in force and progress. A dilatory type of labor usually will stop progressing with this method. The head should be at least to a station 0 or +1 with the presenting part fitting well against the cervix. It has been found that in obese patients a more troublesome hypotension develops, probably due to pooling in the legs and pelvis, and the overweight stocky types have been omitted from this series.

#### Results

In 71 consecutive patients in whom this method was used, 61 obtained complete relief of pain with a level of anesthesia up to the umbilicus. Six patients had partial perineal anesthesia, necessitating a one-sided pudendal block or the addition of a small amount of local infiltration and/or nitrous oxide-oxygen inhalation for the actual delivery. Four patients had relief of the pains of the uterine contractions but obtained no perineal anesthesia and required additional pudendal blocks for delivery. One patient got a good result but the anesthesia wore off before delivery was accomplished. Duration of anesthesia varied from 1½ to 3 hours. The longer durations were obtained when epinephrine in a 1:200,000 dilution was used with the 1 per cent Xylocaine. Included in the 61 cases of complete relief were one Scanzoni maneuver, one immediate postpartum curettage for a retained cotyledon and one manual removal of a placenta. One neonatal death occurred in the case of a gravida ii, para i, in which there was no amniotic fluid except for a few ounces of viscous material. The lungs of this infant failed to expand and it died within

12 hours. The remainder of the deliveries were either by outlet forceps or spontaneous in nature. There were no drug reactions to the anesthetic in this series.

## Comment

The explanation for the phenomenon of profound perineal anesthesia developing from a lumbar sympathetic block has not been determined and must await further investigation. There are two likely possibilities, however. First, this may represent a spread epidurally of the pool of anesthetic agent placed alongside the lumbar spine. However, since this secondary development does not occur unless the delivery table is placed on a slant with the head elevated, it suggests a possible downward spread along fascial planes to the sacral plexus. It is known that Xylocaine as used in this series has a high spreading factor.

# Summary

A technique for producing complete obstetrical anesthesia by means of lumbar sympathetic paravertebral block is described. Seventy-one cases are reported with complete success in 61, partial success in 6, and failure to obtain perineal anesthesia in 4. It is felt that this method could be added to the armamentarium of obstetrical anesthesia.

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# POSTSPINAL HEADACHE IN OBSTETRICS

# A Method of Reducing Its Incidence in the Puerperium

T. R. Sweeney, M.D., E. S. Casey, M.D., E. B. Raheb, M.D., and J. A. Welna, M.D., Boston, Mass.

(From St. Margaret's Hospital and the Department of Obstetrics, Tufts University School of Medicine)

A DEQUATE fluid replacement can reduce the incidence of postspinal headache in obstetrics. The incidence of this form of headache is higher in obstetrical patients receiving spinal anesthesia for vaginal delivery than it is in pregnant and nonpregnant patients undergoing general operations, (including cesarean section).

Vandam and Dripps,<sup>1</sup> in a series of 988 patients delivered vaginally, found a 22 per cent incidence of postspinal headache. These cases were part of a series of 9,277 anesthetizations in both sexes for all types of surgery. The over-all incidence of headache was 11 per cent, or exactly half the incidence that they encountered in vaginal delivery.

Hershenson<sup>2</sup> states that "about 20% to 30% postspinal headaches are seen with vaginal delivery," while Andros<sup>3</sup> reports an incidence of 14.5 per cent. In our study, the incidence of postspinal headache in the control series was 22 per cent.

Various explanations have been offered for the increased incidence in obstetrics. Among the factors cited have been: (1) dehydration associated with the reduced intake and with the increased muscular activity seen in labor; (2) alterations in cerebrospinal fluid pressure due to the variations in intra-abdominal pressure found in labor; (3) the rapid changes in blood volume during and after delivery (physiologic blood loss); (4) the widespread lack of concern with parenteral fluid replacement in the early postpartum period; (5) the role of suggestion in patients of this sex and age group.

The present study postulates that dehydration during labor and blood loss at delivery might be entirely responsible for the increased incidence of headache in obstetrics over that found in general operations. If this is true, restoration of the state of bodily hydration to normal should decrease the incidence of postspinal headaches to the level found in surgery.

Up to now, most of the work in postspinal headache has been directed toward treatment after the headache developed. In this study, an attempt was made to prevent the development of these headaches by promoting adequate bodily hydration at the time of delivery.

#### Definition

A postspinal headache is a type of headache which can occur after any lumbar puncture and which has the following characteristics:

1. It is aggravated by erect posture and improved by recumbency.

2. The time of onset may coincide with assumption of erect posture or it may be delayed as much as five months.<sup>1</sup>

3. The site is variable. It may be frontal, occipital, nuchal, or any com-

bination of these.

4. The severity and duration vary. (Vandam and Dripps¹ found that 19 per cent of headaches in their series persisted longer than a week.)

5. They are more common in women.

6. The greatest frequency is in patients under age 50.

The postspinal headaches encountered in this series were graded as follows:

Grade I (Mild).—A headache present only in the morning, noted over 1 to 2 days, and helped or cleared by mild analgesics such as aspirin or codeine.

Grade II (Moderate).—One which forced the patient to remain flat in bed for 24 to 48 hours. Mild analgesies gave some relief to this group.

Grade III (Severe).—These headaches persisted for more than 48 hours and the usual mild analyssics together with bed rest did not relieve them.

# Pathologic Physiology

There appears to be general agreement that loss of cerebrospinal fluid is responsible for postspinal headache. 1, 4, 5, 6 Cerebrospinal fluid leaks through the hole made in the dura at the time the anesthetic is given. Unless secretion of fluid by the choroid plexus exceeds the amount lost through the perforation

in the dura, the cerebrospinal fluid pressure will drop.

Kunkle, Ray, and Wolff<sup>7</sup> were able to induce the typical postspinal headache consistently in 11 patients by the withdrawal of 20 c.c. of cerebrospinal fluid with the patient erect. They postulate that the fall in intracranial pressure which follows the removal of cerebrospinal fluid in the erect human produces (1) intracranial venous dilatation and (2) an increase in the usually mild and painless traction by the brain on its anchoring structures among which are the above-mentioned (pain-sensitive) dilated veins. Papers published subsequently by other workers including Thorsen<sup>6</sup> in 1947 and Vandam and Dripps<sup>1</sup>

in 1956 are in support of this theory.

Two mechanisms can individually or simultaneously act to lower the cerebrospinal fluid pressure. They are: (1) loss of cerebrospinal fluid (occurring with such conditions as lumbar puncture, brain surgery, or a skull fracture); (2) insufficient formation of cerebrospinal fluid. Flexner<sup>s</sup> proved that cerebrospinal fluid is produced mainly by active secretion and not merely by simple filtration. The choroid plexus is considered to be the main source of cerebrospinal production. Such a process might therefore be altered by such mechanisms as degenerative changes in the choroid plexus, bodily hydration, or by changes in the flow or even the viscosity of the blood passing through the plexus. Furthermore, the autonomic nervous system may eventually be proved to also play a very significant role in the regulation of the production of cerebrospinal fluid.

The administration of spinal anesthesia for delivery creates a passage through which cerebrospinal fluid may be lost. The second mechanism, insufficient formation of cerebrospinal fluid, might be initiated by dehydration resulting from the decreased oral intake found in women during childbirth. In addition to this, women in labor have increased rates of respiration and perspiration.<sup>9</sup> Furthermore, emesis is common. Finally, blood loss in the third

stage contributes further to the decrease in the volume of body fluid. The combination of any or all of these factors might result in dehydration severe enough to curtail the formation of cerebrospinal fluid. At the same time, this dehydration might not yet be evident on clinical examination.

Most of these factors are not operative in the average surgical case. This could explain the discrepancy in the incidence of postspinal headache found in the two groups.

# Material and Method

Five hundred and sixty-eight unselected obstetric patients admitted to St. Margaret's Hospital, Boston, Massachusetts, from October, 1957, to October, 1958, were studied. All were delivered vaginally, and cases of excessive post-partum bleeding (over 500 c.c.) were excluded from the series. In low spinal anesthesia, Pontocaine (tetracaine hydrochloride), 0.3 per cent, was used exclusively, the usual dose being 4.5 mg. in 1.5 c.c. of 6 per cent dextrose in water, a hyperbaric solution. The anesthesia, as a rule, was given with the patient in the lateral decubitus position, the cervix at full dilatation, and, in the case of primiparas, the head was usually presenting. The gauge of needle was limited to size No. 22 or No. 21. Usually the latter was tried when no success was achieved with the former. A physician-anesthetist was on hand 24 hours a day for the administration and supervision of anesthesia. House officers assisted him during periods of increased activity.

The first group (the prophylactic fluid group) received at least 1,000 c.c. of 5 per cent dextrose in water intravenously at or near the time of delivery. The indications for fluid in this group in the early part of the study were mainly induction with intravenous Pitocin and Pitocin drip for postpartum uterine atony. Later, fluids were given solely for the prophylaxis of headache.\*

The second group (the control group) received no intravenous fluids during their hospitalization.

Follow-up studies were confined mainly to the patient's postpartum stay in the hospital. The average duration of this stay was 5 days. Since only 1.5 per cent of the cases of Vandam and Dripps¹ experienced an onset of headache after 6 days, we felt that the interval in the hospital was adequate for the study of a controlled series such as this.

TABLE I. THERAPY AND SEQUELAE

	NO.	%
Prophylactic Fluid Group		
No headache	85	90.5
Headache	9	9.5
Control Group.—		
No headache	371	78
Headache	103	22

The method of follow-up in the postpartum period was designed to avoid suggesting the possibility of headache to the patient. The interrogating physician was cautioned to always mention other symptoms in the sentence (e.g., "Any leg pain, backache, headache, breast pain, or stomach-ache?"). In this way the patient would be forced to choose any symptom(s) causing her discomfort from the group mentioned. It was felt that this method of questioning would not suggest to the patient that headache was being studied as a complication. If headache were admitted, the patient was questioned further to determine whether she had a true "postspinal" type of headache. Only such

<sup>\*</sup>Kindly supplied by a grant obtained through Dr. E. A. Hawk from Mead Johnson & Company, Evansville, Ind.

headaches are included in the statistics. Further questioning at this time and later on in the patient's hospital stay was used to determine the severity of the headache. The pertinent facts concerning the patient, the anesthesia, any method of prophylaxis, and the sequelae were recorded on a form included in every patient's chart upon her admission to the hospital. The patients were usually interviewed without the physician's knowing whether or not they had received prophylactic fluids. However, this information was available to the interviewing physician on the above-mentioned forms. Therefore, this study cannot be considered a true double blind test.

# Results

The incidence of postspinal headache in vaginal delivery ranges from 14.5 to 30 per cent. Our incidence (22 per cent) fell in this range when fluids were withheld. It was below this figure with administration of at least 1,000 c.c. of intravenous fluids at or near the time of delivery, the incidence falling to 9.5 per cent (Table I). These results, as determined by the chi-square formula, were significant (P < 0.01). The degree of involvement also differed. The group with headaches who received fluids had a 22 per cent incidence of moderate (Grade II) headache with no severe headaches encountered, whereas 57 per cent of the control group experienced either a moderate or a severe (Grade II or III) headache (Table II).

TABLE II. TYPE OF HEADACHE

	NO.	%
Prophylactic Fluid Group.—		
Mild	7	78
Moderate	2	22
Severe	0	0
Control Group.—		
Mild	44	43
Moderate	41	40
Severe	18	17

The median time between last intake and delivery for those (9 cases) who developed headache in the prophylactic fluid group was 12 hours. It was 93/4 hours for those (103 cases) who developed headaches in the control group.

# Comment

The widespread use of saddle block anesthesia in obstetrics has been hindered by two fears expressed by many patients. The first of these is the fear that a permanent paralysis may ensue. Vandam and Dripps¹ found that with the use of proper technique major neurologic sequelae could be avoided. The second worry is that they may develop a "spinal headache." The findings of this study seem to support the idea that dehydration is responsible for the increased incidence of postspinal headache found in patients delivered vaginally. The prophylactic measures employed in the series appear to be effective in reducing both the incidence and the severity of postspinal headache.

The theory behind these measures is not new. Weed and McKibben<sup>12</sup> described a rise in cerebrospinal fluid pressure after the intravenous injection of hypotonic saline into cats in 1919. In 1920, Baar<sup>13</sup> used 500 to 750 c.c. of hypotonic (0.5 per cent) saline intravenously immediately after diagnostic lumbar puncture in 7 nonluctics. One headache resulted (14 per cent). In his

control series 44 of 66 (67 per cent) developed headache. Because of the adverse effect of saline noted in obstetric patients, 11 we preferred to use 5 per cent dextrose in water in the present study.

Saddle block anesthesia is superior to inhalation-type anesthesia in many instances. Such cases include patients who have recently eaten, who have respiratory complications, or who have severe diabetes. In the delivery of premature infants, the superiority of this form of anesthesia over general anesthesia is well known. However, it is well to bear in mind the contraindications of the method before deciding to use it in a specific case. Hershenson<sup>10</sup> lists 18 contraindications, including known or suspected central nervous system disease, mental instability, infection at or near the site of puncture, and congenital anomalies in the area, to mention but a few.

The use of intravenous fluids at the time of the administration of saddle block has additional potential advantages. It tends to combat any tendency to hypotension induced by the anesthetic drug, and in the case of postpartum hemorrhage, it provides an already open vein for the administration of plasma expander, and, when available, blood.

# Summary and Conclusions

- 1. The physiology of postspinal headache and its prophylaxis is discussed.
- 2. The use of prophylactic fluid in adequate amounts reduced the incidence of postspinal headache in the series from 22 to 9.5 per cent.
- 3. Using the chi-square formula on the above results, chi was found to be This represents a likelihood of duplication of the results by chance of less than 1 in 100.
- 4. The percentage of headaches classified as moderate or severe was less in the group which received prophylactic fluids than in the control group.
- 5. Other advantages of intravenous fluid administration at delivery are described.

We are indebted to Dr. Daniel J. McSweeney, Professor of Obstetrics, Tufts University School of Medicine, and Chief of Obstetrics, St. Margaret's Hospital, for advice and criticism of this paper.

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2119 DORCHESTER AVENUE BOSTON 24, MASSACHUSETTS

# FULMINATING PRE-ECLAMPSIA WITH CESAREAN SECTION PERFORMED UNDER HYPNOSIS

A Case Report

L. B. Winkelstein, M.D., and J. Levinson, M.D., Mount Vernon, N. Y.

(From the Department of Obstetrics and Gynecology, Mount Vernon Hospital)

HYPNOSIS for obstetrical anesthesia is becoming a more popular procedure. One of us (L. B. W.)¹ has recently published results with hypnoanesthesia in a series of routine deliveries. There is no question but that this type of anesthetic is best and safest for both mother and child. Similarly, hypnoanesthesia has been used for delivery by cesarean section.² As far as can be determined, the surgical procedure was employed more for demonstration than because of absolute medical necessity. It is the purpose of this paper to report a case of severe, fulminating, pre-eclamptic toxemia, in which the patient was delivered by cesarean section and in which hypnosis, resulting in complete absence of pain, was not only the anesthetic of choice, but, for all practical purposes, was the only safe procedure for both mother and child.

Mrs. C. V., No. 260520, a 36-year-old white primigravida, was admitted on Oct. 10, 1958, for evaluation of impending toxemia of pregnancy. The last menstrual period was Dec. 15, 1957, and the estimated date of confinement was calculated as Sept. 22, 1958. She stated that she was approximately 2 weeks overdue.

Past history included scarlet fever at 9 years of age without sequelae. She had had no operations and there was no history of glomerulonephritis, pyelonephritis, diabetes, or cardiac disease. In 1952, after a routine examination for weight control, she was told she had moderately high blood pressure. She had been married 4 years. Prepregnancy weight varied between 230 and 242 pounds.

The first 5 months of gestation were uneventful. Blood pressure remained around 140/90 mm. Hg and weight gain was 13 pounds. From the end of the fifth month to the beginning of the ninth month, the blood pressure varied between 140/90 mm. Hg and 180/100 mm. Hg, and on 3 occasions proteinuria was noted. Weight gain averaged 1 pound per week despite a controlled, salt-free diet. During the ninth month there was a weight gain of 21½ pounds (9½ of them during the 5 days preceding admission); an increasing elevation of the blood pressure; and progressively increasing amount of proteinuria. Also, the patient complained of severe headache and nausea.

Physical examination on admission revealed a markedly obese woman weighing 287 pounds, who was extremely apprehensive and lethargic. The blood pressure was 190/130 mm. Hg; pulse, 80 per minute; respirations, 20 per minute. The face, hands, ankles, and presacral areas were markedly edematous. The pupils were equal and reacted equally to light and accommodation. The head, neck, heart, and lungs were normal. The abdomen was protuberant and contained an enlarged gravid uterus which extended to  $1\frac{1}{2}$  fingerbreadths

below the xiphoid. Fetal parts were difficult to outline. The vertex was ballotable over the inlet. Examination of the nervous system showed all reflexes to be bilaterally hyperactive. Kernig and Babinski reflexes were absent. Examination of the eye grounds revealed slight blurring of the left disc. Sterile vaginal examination showed the cervix to be 2 cm. dilated, uneffaced, hard, and posterior. The vertex was unengaged. Laboratory findings on admission were as follows: hemoglobin, 10.4 Gm., red blood count, 3.67 million per cubic centimeter, white blood count, 13,850 per cubic centimeter with a normal differential, hematocrit 31 per cent; catheterized urine: specific gravity, 1.030, acid, albumin 4 plus, glucose 1 plus, acetone negative; microscopic: many red blood cells and white blood cells and occasional hyaline casts. The nonprotein nitrogen was reported as 36 mg. per cent; creatinine 2.0 mg. per cent; glucose 92 mg. per cent; albumin 3.15 Gm.; globulin 1.6 Gm.; total protein 4.75 Gm.

A diagnosis of severe pre-eclampsia was made. Therapy was started immediately and consisted of complete bed rest, a salt-free diet, measurement of intake and output, and recording of blood pressure and pulse every 2 hours. Magnesium sulfate, 4 c.c. of a 50 per cent solution, and morphine sulfate, 1/4 grain, were given immediately and repeated at 4 hour intervals. Chlorothiazide (Diuril), 500 mg., was administered twice daily, and reserpine (Serpasil), 0.25 mg., at 4 hour intervals. The patient was closely observed for 24 hours, during which time the blood pressure rose steadily to a peak of 230/160 mm. Hg despite therapy, and the total amount of urine excreted was less than 350 c.c. Despite the intravenous administration of 25 Gm. of human albumin, the facial and presacral edema increased. The patient complained of increasingly severe headache and nausea and vomited several times. Reflexes had become still more hyperactive, and small generalized ephemeral twitching was seen. In view of inability to control the toxemic process, and because of the fulminating nature of the disorder, immediate termination of the pregnancy was deemed necessary. Since the cervix remained nonnegotiable, the abdominal route for delivery was elected. X-ray of the abdomen confirmed the presence of a single fetus, vertex presentation, without engagement of the fetal head. The fetal heartbeat remained regular at 144 per minute.

Since both general and spinal anesthetics were deemed hazardous, and since it was felt that, in view of the patient's extreme obesity and nervous irritability, the pain of local infiltration might precipitate a convulsion, hypnoanesthesia was attempted. Although she had had no previous training, the patient was easily hypnotized with the authoritarian technique. Complete anesthesia below the costal margin and immobility of the arms, torso, and legs were also easily developed. The patient was then taken to the operating room, where the suggestions were reinforced. Anesthesia was proved by pinching the skin with Kelly clamps and tenacula. After sterilization of the skin and draping, a low flap cesarean section was performed with ease and with complete absence of pain. During the entire operation, suggestions were continued. A living male infant weighing 8 pounds, 9 ounces, who cried spontaneously, was delivered. Hypnoanesthesia continued after delivery and both the uterine and abdominal wounds were completely repaired with only the addition of exceedingly small amounts of nitrous oxide.

Before the hypnotic trance was induced the blood pressure was 230/160 mm. Hg and it remained at that level until the baby was delivered. It then descended to 180/120 mm. Hg and stayed there for 24 hours. It subsequently dropped slowly until on the third postpartum day it was 130/94 mm. Hg, which was approximately the prepregnancy level. We do not feel that the hypnotic trance had any effect whatsoever on the blood pressure.

Until the eighth postpartum day, the postoperative course was relatively uneventful. The blood pressure descended to prepregnancy levels on the third day and remained there with minor fluctuations, until discharge. There was some paralytic ileus which was treated by Cantor tube and Wangensteen suction on the second and third days and which disappeared on the fourth day. Urinary output on the first day was 400 c.c.; on the second day 950 c.c.; and on the third day 950 c.c. On the fourth day an intense diuresis set in and signs of potassium deficiency were noted and confirmed by electrocardiogram. This was remedied by the oral administration of potassium salts. On the eighth day, however, after removal of the

sutures, a serosanguineous discharge appeared in large quantities and continued, without breakdown of the wound, for 2 days. It was felt that a separation of the deep layers had developed and that a possible evisceration might occur. Therefore, exploration and revision of the wound was deemed necessary.

It was thought that since hypnoanesthesia was so satisfactory for the original operation, it might be employed to advantage a second time. The patient, however, during the previous 8 days had practically been on exhibition. Hypnosis was not only constantly discussed in her presence, but she was also subjected to much questioning with a focus centering on the unique and miraculous nature of the procedure. As a result of this, her orientation and feelings changed. Although she still wished to be cooperative, she no longer could accept hypnosuggestions and demanded spinal anesthesia.

Under spinal anesthesia the wound was opened. The fascia and peritoneum were found to be intact. There was, however, a great deal of fatty necrosis present which was causing the discharge. This was débrided and the wound closed. The remainder of the hospital stay was uneventful, and the patient was discharged from the hospital on the nineteenth postpartum day.

#### Comment

This case presented a picture of fulminating pre-eclamptic toxemia with failure of medical control and with delivery by cesarean section. It is unique, however, in several aspects.

First is the importance of the anesthetic agent employed for the section. After the decision was reached to operate, the problem was discussed with the anesthetist. It was felt that general anesthesia presented too great a threat to the baby and, therefore, should not be used. Similarly, because of the extreme elevation of the blood pressure and especially the diastolic blood pressure (230/160 mm. Hg), spinal anesthesia was discarded because of the possibility of the development of hypotension. Local infiltration anesthesia was also considered hazardous. It appeared that the extra stimulation of local injection might precipitate a convulsive seizure since tremor of the hands and legs was already present. This left hypnoanesthesia as the safest procedure.

Second was the ease of induction of the trance state and the absolute acceptance by the patient of suggestions of absence of pain and inability of motion. No more than 4 minutes were spent in induction and not more than an additional 2 minutes for the development of complete anesthesia. This was felt to be due to (1) the recognition by the patient of the seriousness of her condition; (2) the confidence of the patient in her physician and obstetrician; (3) the maximal desire to cooperate; (4) the maximal desire to recover; and (5) the complete ignorance of the type of procedure which was to be employed. The psychiatric, psychosomatic, and psychological aspects of this will be discussed in a subsequent paper.

Third, was the failure to develop hypnoanesthesia for the surgical revision of the wound. Maximal incentives were offered but, although a hypnotic trance was induced, the development of anesthesia both by direct and by indirect suggestion was rejected. As has been explained, this was probably due, basically, to loss of confidence in the procedure, a confidence which could not

be revived in spite of the expenditure of considerable amounts of time. This, we feel, presents an interesting highlight and, as yet, a poorly explored area in the field of hypnosis in general, and of hypnoanesthesia in particular.

We wish to thank Dr. Charles Danetz for his early management of the case and Dr. Ray Arcuri for his cooperation with the problems of anesthesia.

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# HEMANGIOMA OF THE UTERINE CERVIX COMPLICATING PREGNANCY\*

A Case Report

B. FRANK LOVETT, M.D., CAMDEN, N. J.

(From the Department of Obstetrics of The Cooper Hospital, Camden, N. J., and the Department of Obstetrics and Gynecology, Jefferson Medical College and Hospital, Philadelphia, Pa.)

TRUE hemangiomas are thought to be of congenital origin, arising by embryonic sequestration of mesodermal tissues. Because of their origin, they may involve any structures of the body including mucous membranes, liver, lungs, heart, brain, and, most commonly, the skin. They are usually present at birth and may retain their original size, grow with the body, or show accelerated growth leading to destruction of surrounding tissues.

Hemangiomas involve the female genitals rather rarely, but have been observed in the ovaries, Fallopian tubes, uterine corpus, endometrium, round ligaments, and vulva. Gerbie<sup>3</sup> in 1955 reviewed the literature and noted 27 cases of hemangioma of the uterine corpus and endometrium. He reported 3 additional cases involving the myometrium and one, the ovary. Mandelstamm<sup>4</sup> reported the case of a 25-year-old primigravida with a hemangioma attached to the left cornu of the uterus, treated by excision during the first trimester of pregnancy.

A hemangioma less often involves the cervix. Wirth<sup>5</sup> described one patient observed through 2 pregnancies who developed a telangiectatic hemangioma of the cervix which was apparent only during pregnancy and disappeared promptly after delivery. Nobrega and Salvatore reported on a patient who experienced vaginal bleeding for 8 months following vaginal delivery; biopsy of a cervical erosion and amputation of the cervix established the diagnosis of hemangioma of the cervix. Nigro and Tabaka<sup>7</sup> reported the case of a 29-yearold primigravida with a polypoid lesion of the cervix which revealed a plexiform arrangement of blood vessels compatible with hemangioma. Treatment by cauterization produced satisfactory results and the lesion was absent 6 months postpartum. Bretteville-Jensen's reported the case of a 27-year-old secundigravida with a large, soft tumor of the cervix which almost filled the vagina. Four months subsequent to successful delivery, the hemangioma was excised by cervical amputation. Voight reported a case of hemangioma of the cervix in a 23-year-old woman who had had 2 normal pregnancies. Weed<sup>10</sup> reported the case of a 39-year-old primipara on whom a vaginal hysterectomy

<sup>\*</sup>Read at a meeting of the Obstetrical Society of Philadelphia, April 3, 1958.

was performed 9 years after delivery; microscopic examination of the cervix revealed a cavernous hemangioma involving the portio vaginalis. Brandfass and Scheffey<sup>11</sup> in 1955 reported an additional case and referred to 7 cases in the literature, including those of Nigro and Nobrega; all patients in their report had at least one child. If we assume that hemangiomas are congenital lesions, then pregnancies must have occurred one or more times in 12 women with such lesions. The extent of the lesion at the time of delivery and the changes which occurred subsequent to delivery are not always clear. Delivery by cesarean section is not discussed.

E. S., a 23-year-old primigravida, was first seen in the office on June 24, 1955. The last menstrual period had occurred on March 23, 1955, and the estimated date of confinement was Dec. 30, 1955. She had had the usual childhood diseases but no serious illness and no operations. Premarital physical examination in 1952 had revealed "an odd lesion of the cervix which was not an erosion," but a biopsy was not performed. The patient abandoned the use of a contraceptive diaphragm early in her marital life because its use was usually associated with postcoital bleeding. The menarche occurred at 12 years, and menstruation occurred regularly every 28 days; the duration of flow was 8 days and was considered to be of average quantity. Vaginal tampons were used without producing abnormal flow.



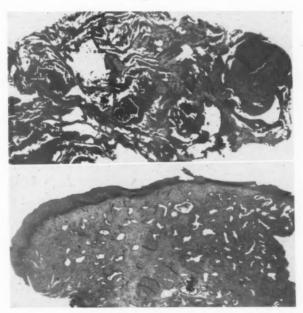


Fig. 2.

Fig. 1.—Photomicrograph of biopsy of lower segment of uterus. Note the numerous dilated blood spaces lined by a single layer of endothelium and supported by a loose stroma. Fig. 2.—Photomicrograph of biopsy of cervix. The squamous epithelium is normal. The underlying stroma is rich in rather large blood spaces lined with endothelium.

Pelvic examination revealed normal external genitals and a nulliparous vagina. The cervix was approximately 4 cm. in its transverse diameter. An elevated, purple lesion, approximately 2 cm. in diameter, extending outward from the external os, and occupied the right

half of the anterior lip of the cervix. This was soft to the touch and not nodular. There was no evidence of cervicitis or erosion. The uterine corpus was the size of a 12 weeks' gestation. Laboratory studies, including a vaginal cytological smear, were normal.

The patient progressed through a normal pregnancy. The cervix was examined repeatedly and was observed to become tremendously enlarged, softened, and vascular. At term it measured approximately 8 cm. in its transverse diameter and insertion of a vaginal speculum was sufficient to cause a transudation of a serosanguineous fluid through the thinned squamous epithelium.

Cesarean section was performed on December 29. The bladder flap of peritoneum was first reflected and revealed what appeared to be a normal lower uterine segment. A longitudinal incision was made and an 8 pound, 6 ounce, female infant delivered. The lower segment, which was unusually thickened by a spongy, vascular tissue filled with thrombi, was subjected to biopsy.

The patient made an uneventful recovery. At examination on the eighth postoperative day, the cervix was found to be rapidly returning to its prepregnancy state and measured 2 cm. in its transverse diameter. A purple, elevated lesion surrounded the os for 1 cm. on its anterior lip. A biopsy was made of this.



Fig. 3.—Appearance at colposcopic examination, nonpregnant.

Histological examination<sup>13</sup> of the tissue of the lower segment of uterus was reported as "consisting essentially of widely dilated blood spaces lined by a single layer of endothelium and supported by a loose, fibrous tissue" (Fig. 1). These changes were regarded as consistent with either a cavernous hemangioma or varix. Two sections of cervix were studied and the following description made: "The underlying connective tissue is rich in rather large blood spaces, lined with endothelium. The appearance is that of a hemangioma and is entirely benign." (Fig. 2).

The patient resumed normal menstrual function, and periodic examinations were normal except for the cervix. Colposcopic examination<sup>14</sup> in May, 1956, revealed no significant abnormality except for the circumscribed vascular lesion of the cervix (Fig. 3). Vaginal cytological examination at this time was normal.

The patient remained in good health and was asymptomatic except for occasional episodes of postcoital bleeding. Periodic examinations revealed no evidence of enlargement of the lesion. She became pregnant in December, 1956, and was delivered by elective repeat cesarean section in August, 1957. The cervix was observed to undergo the same changes as had occurred during the first pregnancy, except that the changes were less profound. At the time of the laparotomy, the hemangioma of the lower segment was absent, apparently having been destroyed by thrombosis during the first pregnancy.

# Summary

A case of hemangioma of the cervix is presented along with the course of the patient through pregnancy and delivery by cesarean section.

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CAMDEN, N. J.

# VAGINITIS EMPHYSEMATOSA

# A Case Report

DAVID B. HOFFMAN, M.D., AND PHILLIP GRUNDFEST, M.D., NEWARK, N. J.

(From the Department of Obstetrics and Gynecology, Newark Beth Israel Hospital)

VAGINITIS emphysematosa is a rather rare condition which occurs most often in pregnant patients although occasional cases have been reported in nonpregnant women.<sup>1</sup>

The present case is being reported because of the rarity of the condition and because an attempt was made to determine the exact nature of the gas in the lesion. Neither the etiology of the condition nor the type of gas in the lesion is known. Some authors believe that the lesion is associated with bacteria of the coliform group which disappear as gas formation distends the cysts.

Gardner<sup>2</sup> reported that the gas is endogenous. Nagashima<sup>5</sup> maintained that the condition arose in the epithelium and later penetrated into lymph spaces where the gas was found. Thus, epithelium nests formed followed by liquefaction and gas formation.

Ingraham and Hall<sup>3</sup> attempted to inject cultures from these cysts into the vaginal walls of rabbits and guinea pigs and obtained an inflammatory reaction but were not successful in reproducing emphysematous vaginitis. When the vaginas of pregnant women were swabbed with secretion from patients with emphysematous vaginitis, the condition was not reproduced.<sup>1, 3</sup>

Vaginitis emphysematosa is characterized by the appearance of a tumorlike lesion attached by a broad base to the cervix or upper part of the vagina or both. Within this tumefaction, there are multiple small cysts which vary in size from several millimeters to several centimeters. When these cysts are opened, the contained gas escapes.<sup>1</sup>

The disease is self-limited, and disappears within a few months or weeks post partum.<sup>1</sup>

A. B.,\* a 21-year-old gravida 0, presented herself at the Obstetrical Clinic because of vaginal bleeding for 3 months. She had been seen by her local physician who made a diagnosis of pregnancy and a "ragged neck womb." The last menstrual period was Aug. 5, 1957. The vaginal bleeding was reported worse after sexual intercourse. On examination, a large tumorlike mass was seen which bled easily to the touch, and which contained multiple cysts (Fig. 1). This mass involved the anterior lip of the cervix and the vaginal wall. It

<sup>\*</sup>This case was from the Ward Service of Dr. W. Brams, Chief Obstetrician-Gynecologist of Newark Beth Israel Hospital.

was soft, almost gelatinous, and contained numerous small cystic domes. The patient was admitted to the hospital and on Dec. 8, 1957, under Pentothal Sodium anesthesia, a large section of the mass was removed. The pathological report was "squamousmucosal and submucosal tissue containing apparently gas-filled cysts. There is surrounding acute inflammation. Note: This lesion would seem most consistant with so-called vaginitis emphysematosa, however, the foreign-body giant cell reaction usually described was absent in these sections and the cavity was lined by flattened fibroblasts" (Fig. 2).

The patient was discharged from the hospital Dec. 31, 1957, undelivered. She was readmitted April 9, 1958, in active labor and was delivered spontaneously. No difficulty from the lesion was encountered and at delivery another large biopsy specimen was taken. This was sent to the laboratory for analysis of the gas.



Fig. 1.—Gross appearance, vaginitis emphysematosa.

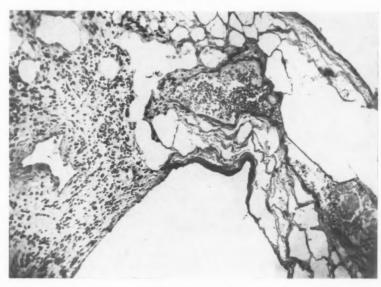


Fig. 2.—Microscopic appearance, vaginitis emphysematosa. (Hematoxylin and eosin.  $\times 150$ ; reduced  $\frac{1}{2}$ .)

The excised gas cysts were cut open under water and the escaping gas (approximately 5 ml.) was collected through an inverted funnel into a test tube.

The standard test for gas analysis was followed. The gas was tested with solutions of calcium hydroxide and sodium hydroxide for the presence of carbon dioxide, and with lead acetate for the presence of hydrogen sulfide. There was no precipitation with the lead acetate, even under ×10 magnification, indicating the absence of hydrogen sulfide. Precipitation with calcium hydroxide and the absorption of the gas by sodium hydroxide indicate the presence of carbon dioxide as the gas recovered from the cysts of the lesion. The volume of carbon dioxide contained in the gas recovered from the lesion was 8 to 20 per cent.

The patient was subsequently seen in the outpatient department 6 weeks postpartum and the lesions of the vagina and cervix had spontaneously regressed.

# Summary

A case of vaginitis emphysematosa is described. The gas in the cystic lesions was found to be carbon dioxide. The cause of the condition is unknown. The lesions regressed spontaneously.

We wish to thank Dr. Lester Goldman, Director of Laboratories at Newark Beth Israel Hospital and Dr. J. Keosin, Professor of Biology at Rutgers State University, for their technical assistance in the preparation of this paper.

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NEWARK, N. J.

# GIANT HYDRONEPHROSIS COMPLICATING PREGNANCY\*

R. L. BERNSTINE, LIEUTENANT COMMANDER (MC) USN,

G. A. LEBLANC, LIEUTENANT (MC) USN, AND

J. F. RICHARDSON, CAPTAIN (MC) USN

(From the United States Naval Hospital, St. Albans, Long Island, New York)

THE coexistence of giant hydronephrosis and pregnancy is a rare condition. Crabtree¹ reported the case of a primiparous patient who had had a renal mass since the age of 1½ years and who refused treatment until she was pregnant. Superimposed infection made operation necessary. Nephrectomy was performed and the removed kidney (dilated to capacity) measured 36 by 21 cm.

Hecht<sup>2</sup> presented a case which was diagnosed preoperatively as an ovarian cyst complicating pregnancy. At the time of laparotomy a large hydronephrotic kidney was removed which measured 15 by 20 cm. and contained 5,300 c.c. of clear urine.

Other case reports<sup>3, 4, 5</sup> discussed the general subject of kidney masses complicating pregnancy and presented cases in which smaller hydronephrotic kidneys were found and treated, either by nephrectomy or nephrostomy.

An additional case is reported in which a large renal mass was discovered and removed successfully during the course of the pregnancy.

#### Case Report

A 19-year-old white woman was seen initially on Feb. 5, 1957, complaining of constipation of 4 days' duration and a dull aching sensation in the left lumbar region for a similar period of time. The last normal menstrual period was July 31, 1956; the estimated date of confinement May 9, 1957.

The past medical history was noncontributory save for a heart murmur since the age of 3 years. Physical examination revealed a Grade III blowing systolic murmur which was audible over the entire precordium with maximum intensity over the pulmonic area. The blood pressure was 110/80. The abdomen was enlarged by the presence of the pregnant uterus (6 months' gestation) and a semifirm, regular mass which occupied the entire right side of the abdomen and extended into the pelvis. It displaced the uterus to the left. Urine specimens contained many leukocytes and culture produced alpha streptococcus. An intravenous urogram demonstrated a normally functioning left kidney and a nonfunctioning right kidney. Retrograde studies on the right side were unsuccessful because of reflux down the ureter from the obstructed area. The right ureter was deviated across the midline by this mass on the right. The impression was of a large hydronephrotic nonfunctioning right kidney.

<sup>\*</sup>The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the view of the Naval service at large.

A chest x-ray disclosed prominence of the left pulmonary segment with enlargement of the cardiac silhouette to the left representing a markedly enlarged right ventricle pushing the apex up. The electrocardiogram was normal except for sinus tachycardia. The tentative diagnosis was intra-atrial septal defect.

Right nephrectomy was performed on Feb. 9, 1957, through a right lumbar incision.

Pathologic Report.—

Macroscopic: The specimen consisted of a large kidney-shaped cystic mass, the surface of which was lobulated. The mass weighed 6,000 grams and the approximate

Fig. 1.

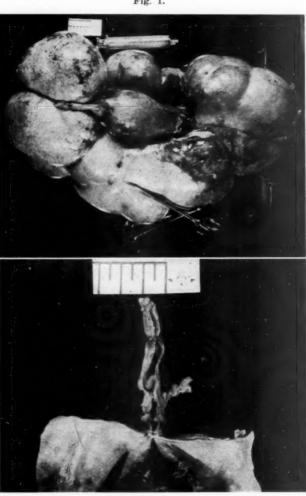


Fig. 2.

Fig. 1.—Large hydronephrotic kidney.

Fig. 2.—Opened kidney pelvis with attached ureter showing valvelike areas of obstruction.

measurements were as follows: 37 by 22 by 12 cm. Prior to submission the surgeon had removed 6,100 c.c. of urine. He had replaced it with saline. The mass when opened was found to be composed of multiple cystic masses which, however, communicated. The

wall was paper thin, smooth, and glistening on both surfaces and translucent. No normal kidney parenchyma was grossly noted. The renal pelvis was dilated to approximately 7 cm. across. There was attached a portion of ureter which measured 6 cm. in length. When this was opened there was a valvelike obstruction which appeared complete at the ureteral-pelvic junction; 2 cm. distal to this there was a similar valvelike obstruction which was not complete.

Microscopic: Examination revealed sections of a cyst wall to be composed of dense collagenous tissue in which there were scattered remnants of glomeruli and tubules. These were, however, quite rare. The glomerular tufts contained blood in some areas and in these cases Bowman's capsule was quite thin and normal appearing. Sections through the pelvis and ureter showed it to be composed of a thin layer of stratified squamous epithelium. There was infiltration of the muscular wall of the ureter with mononuclear cells.

Diagnosis.—Hydronephrosis of the right kidney, secondary to mucosal valvelike obstruction of the ureter.

Subsequent Course.—The immediate postoperative course was complicated by moderate anemia and slightly elevated blood urea nitrogen. Intravenous fluids and blood transfusions corrected these conditions. The pregnancy was not disturbed and fetal heart tones remained unchanged. The patient was discharged on the tenth postoperative day.

On subsequent prenatal visits a normally enlarging uterus was observed. Urinary function was normal as evidenced by normal urinalyses and blood urea nitrogen determinations.

At term the fetal head engaged but labor did not ensue for a period of 4 weeks. Medical induction was successful and a living female infant was delivered by low forceps.

On the third day of life the infant developed a bacterial meningoencephalitis which responded slowly to antibiotic therapy. Subsequently, development of the infant was markedly retarded.

Six months following delivery the renal status of the mother was satisfactory,

#### Summary

- 1. A case of giant hydronephrosis complicating intrauterine pregnancy is presented.
  - 2. In a review of the literature two previous case records were found.

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# PHEOCHROMOCYTOMA DIAGNOSED AT CESAREAN SECTION FOR LABOR OBSTRUCTED BY PELVIC NEUROFIBROMA

F. M. SHELL, M.D., AND MICHAEL NEWTON, M.D., JACKSON, MISS.

(From the Department of Obstetrics and Gynecology, University of Mississippi School of Medicine)

PHEOCHROMOCYTOMA is of great interest both because of its dramatic clinical picture and because valuable physiological information can be obtained from careful study of its secretions. Although it most commonly occurs between the ages of 20 and 40, it is unusual to find it associated with pregnancy. Also, it is occasionally accompanied by generalized neurofibromatosis. The present case is being reported because the presence of a concomitant neurofibroma in the pelvis caused dystocia. A cesarean section was necessary and at this time the diagnosis of pheochromocytoma was made.

# Case Report

E. L. T., University Hospital No. 36254, a 39-year-old Negro woman, gravida vii, para vi, was referred to the Antepartal Clinic of the University Hospital by her local health department on Aug. 1, 1958. The date of the last menstrual period was uncertain but the expected date of confinement was about Oct. 1, 1958. Her previous deliveries had occurred at home under the care of a midwife and had apparently been uncomplicated. Her largest baby had weighed about 10 pounds, and her last child had been born in 1955. She gave no history of hypertension, serious illness, or operations. Generalized skin nodules had appeared at the time of her first pregnancy and had persisted. Upon examination she was thought to be about 7 months pregnant. The total weight gain had been 21 pounds. The blood pressure was 124/80. Generalized skin nodules having the characteristics of neurofibromas were noted. On vaginal examination the pelvis was thought to be adequate for vaginal delivery, but a mass of indeterminate size was felt at the level of the pelvic brim posteriorly and on the left side. This was thought possibly to be a neurofibroma.

The patient made 9 subsequent visits to the Antepartal Clinic, the last being on October 6. She gained an additional 7 pounds in weight. The blood pressure ranged from 120 to 130 systolic and from 65 to 85 diastolic. The urine remained negative for sugar and albumin. Laboratory studies showed a negative serology; hemoglobin, 11 Gm.; hematocrit count, 36 per cent; blood, type B, Rh positive. Chest x-ray examination showed no abnormalities.

On Oct. 11, 1958, she was admitted to the delivery suite at 11:30 a.m. in early labor. Her general condition was good and her blood pressure was 136/92. Rectal examination revealed a vertex presenting at station minus 3 with the cervix 70 per cent effaced and 2 cm. dilated. The membranes were intact. Fetal heart tones were present in the right lower quadrant of the abdomen at a rate of 160 per minute, and the fetus was thought to be slightly above average in size. During the next 12 hours the quality of the labor improved

slowly. The blood pressure remained at about the same level, the highest reading being 150/90. Vaginal examination 11 hours after admission showed the cervix to be 4 cm. dilated with the head still high. X-ray pelvimetry was obtained because of failure of the head to become engaged. Measurements by the Colcher-Sussman technique indicated a possible mild inlet contraction with the anteroposterior diameter of the inlet measuring 10.5 cm. The other measurements were well within normal limits. Fourteen hours after admission, in an attempt to improve the labor, intravenous oxytocin was given cautiously (1 ampule in 1,000 c.c. of 5 per cent glucose in water). Seventeen hours after admission the cervix was 6 cm. dilated but the head still was not engaged. The membranes ruptured spontaneously at this time. The oxytocin was stopped but labor continued and was of moderate intensity. Finally, 20 hours after admission, when there had been no further progress in descent of the head, it was decided to perform a cesarean section. The indication for the section was borderline cephalopelvic disproportion with possible obstruction from a pelvic neurofibroma. During the last 5 hours of labor considerable variation was noted in the blood pressure, which ranged from 128/88 to 190/100.

Cesarean section was performed under Pontocaine spinal anesthesia. Shortly after administration of the anesthetic, the blood pressure showed marked fluctuations. Readings as high as 230/120 were noted on more than one occasion. At this time the possibility of the presence of a pheochromocytoma was entertained. A transverse lower segment cesarean section was performed with delivery of a 7 pound, 10 ounce, living normal male child which breathed and cried immediately. After repair of the uterus and bilateral tubal ligation (for multiparity), the left pelvic mass was palpated and determined to be retroperitoneal, about 4 by 6 cm. in size and lying in front of the left sacroiliac joint. It could be displaced downward into the pelvis and might well have been an obstruction to the descent of the head in labor. Palpation of the right kidney revealed a mass about 4 cm. in diameter situated at the superior pole. Light pressure on this produced marked elevation of the blood pressure. No mass was felt above the left kidney nor was any change in blood pressure noted on palpation in this area or over the pelvic mass. The sudden hypertension was followed by a marked fall in blood pressure to hypotensive levels. Because the patient had not been prepared for removal of the pheochromocytoma, the abdomen was closed in layers in routine fashion. Postoperatively the patient did well and maintained a normal blood pressure until her discharge on the sixth postpartal day.

The patient was readmitted to the hospital on the General Surgical Service on Nov. 4, Her general condition had remained satisfactory. Routine laboratory studies were normal. Fasting blood sugar was 108 mg. per cent, nonprotein nitrogen 32, and an electrocardiogram was within normal limits. Chest x-ray was again normal and x-ray examination of the abdomen showed no evidence of soft tissue masses. Confirmatory evidence of the presence of a pheochromocytoma was obtained from a strongly positive histamine provocative test. After injection of 0.025 mg, of histamine phosphate, the patient had a brief fall in blood pressure followed by a marked rise to 230/110. At this point she complained of severe headache and chest pain. Fifty mg. of phentolamine methanesulfonate (Regitine) was injected intravenously and within 60 seconds the blood pressure began to fall and became stable in 30 minutes. Studies of the catechol amines during the test were of interest and are being reported in detail elsewhere. In summary, the levels of epinephrine and norepinephrine were normal prior to the injection of histamine, rose to several times the normal level immediately following injection, and then fell to relatively normal levels 5 minutes after the administration of Regitine. Except for this test, the patient's blood pressure remained at normotensive levels during the 3 days before operation. Operation was performed on Nov. 7, 1958. Under general anesthesia a right subcostal incision was made and a tumor at the superior pole of the right kidney, 3.5 cm. in diameter, was removed. The mass in the left side of the pelvis was excised from the retroperitoneal area, an appendectomy was performed, and one of the skin nodules was removed for biopsy. During the procedure the patient's blood pressure was maintained with Regitine and ephedrine. As the tumor was manipulated there was a marked rise in blood pressure which returned to normal following complete excision. Postoperatively, the blood pressure remained in the range of 130 to 140 systolic and 70 to 80 diastolic. The subsequent course was uneventful. Pathological examination of the specimen showed a pheochromocytoma of the right adrenal gland with no evidence of malignancy, neurofibroma of pelvic region, neurofibroma of skin, and acute periappendicitis.

#### Comment

When pregnancy is complicated by pheochromocytoma the maternal mortality is high. Of 32 cases collected from the literature by Dean, 16, or 50 per cent, terminated in death of the patient. Most of the difficulty was in the lack of early diagnosis. This was not made initially in 30 of the 32 patients, and in 13 of the 16 patients who died, the condition was not diagnosed until autopsy.

The diagnosis of pheochromocytoma presents a problem even when the patient is not pregnant. In the first place, it is uncommon. Graham² found it in 0.47 per cent of 1,700 patients operated on for essential hypertension. Secondly, the clinical picture is variable.³ The symptoms produced appear to depend upon the proportions of norepinephrine and epinephrine produced by the tumor. If norepinephrine predominates, paroxysmal or sustained hypertension occurs and the metabolic changes are not marked. When more epinephrine is produced there is increased metabolism and hyperglycemia while tachycardia and hypertension are less prominent. The most characteristic symptom complex is that of sudden episodes of headache, apprehension, nervousness, nausea and vomiting, excessive sweating, palpitation, dizziness, and blurring of vision associated with hypertension. These attacks may be precipitated by almost any kind of stimulus including changes in position and pressure on the tumor.

During pregnancy, pheochromocytoma may masquerade as pre-eclampsiaeclampsia, hypertensive cardiovascular disease, or hypertension due to renal disease. Unless typical paroxysmal hypertension occurs, the differentiation of pheochromocytoma from these conditions may be very difficult on the basis of the clinical picture alone. In the case presented here the patient showed no obvious symptoms until subjected to the stress of a long labor.

Laboratory studies are of some help in making the diagnosis of pheochromocytoma. Elevated fasting blood sugar, a diabetic glucose tolerance curve, or increased basal metabolism may occur. In pregnancy, however, these may well be due to other causes. X-ray studies in the form of intravenous pyelograms, retrograde pyelograms, or perirenal air studies may be helpful. In pregnancy, however, the danger of exposing the fetus to unnecessary radiation discourages the early use of these studies. More specific tests include the histamine provocative test, the Regitine and Dibenamine tests, and the detection of epinephrine and norepinephrine or their end products in blood or urine. The histamine provocative test may be of value in the patient with a normal blood pressure who is subject to paroxysmal attacks of hypertension, but it is not without danger in pregnancy. Regitine and Dibenamine tests are applicable to patients with sustained hypertension, although their interpretation is sometimes uncertain. In this case the histamine provocative test was strongly positive. Further, the detection of increased amounts of epinephrine and norepinephrine during the paroxysmal hypertension resulting from the test was well demonstrated in the present case.

If the diagnosis can be made with reasonable certainty, the tumor should be removed as soon as possible, irrespective of the stage of gestation. Although the operative mortality is not inconsiderable<sup>2</sup> the stress of labor and delivery may be much more dangerous. The necessity of having the patient

under adequate control during the operation has been emphasized by many authors. In particular, sudden hypertension associated with manipulation of the tumor requires immediate control with Regitine, and the hypotension which frequently follows removal requires support of the blood pressure with pressor agents.

In the case reported here a combination of fortuitous circumstances made the diagnosis possible. No suspicion of a pheochromocytoma was entertained during pregnancy since the patient was normotensive and had no symptoms. Even during labor, when the patient's blood pressure rose to levels of 190/100, it was assumed that she had underlying hypertensive cardiovascular disease or possibly pre-eclampsia. It was only when marked fluctuations in blood pressure occurred shortly after the administration of anesthesia for cesarean section that the possibility of pheochromocytoma was considered. Ample confirmation of this suspicion was obtained by the discovery of a tumor above the right kidney and the production of paroxysmal hypertension on light palpation of the mass. The decision not to attempt removal at the time of cesarean section was based on the fear of additional trauma to the patient after prolonged labor and the lack of adequate preparation for controlling the blood pressure.

An additional point of interest lay in the obstructive labor due to the pelvic neurofibroma. The patient had been delivered of 6 babies previously, apparently without trouble. At the time of cesarean section it was apparent that the relatively small tumor in the region of the left sacroiliac joint added an additional constriction to a pelvic inlet which was at the lower limit of normal and this probably accounted for the fact that the fetal head did not engage properly.

# Summary

1. A case of pheochromocytoma complicating pregnancy is reported in which the diagnosis was made at the time of cesarean section for obstructive labor due to a neurofibroma in the pelvis. The diagnosis was confirmed by subsequent chemical tests and the tumor was later removed successfully.

2. Although rare, the possibility of pheochromocytoma as a cause of hypertension in pregnancy should always be considered, and appropriate diagnostic tests performed when indicated.

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# PNEUMOMEDIASTINUM AND ASPIRATION PNEUMONIA COMPLICATING LABOR

ROBERT P. EISINGER, M.D.,\* AND HOWARD BERK, M.D., NEW YORK, N. Y.

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(From the Departments of Medicine and Obstetrics, Beth Israel Hospital)

PNEUMOMEDIASTINUM is an unusual complication of parturition. Gordon¹ was able to find only 130 cases reported before 1927. Occasional reports have appeared since his survey.²-⁵ We have been unable to find a previous case in which aspiration pneumonia coexisted with pneumomediastinum, and Faust⁶ stated in 1940 that no such instance had been reported. Consideration of the rarity of the condition and the unusual differential diagnostic problem posed by the following case prompted this report.

# Case Report

A vigorous, healthy, 20-year-old white primigravida had an uneventful pregnancy except for recurrent heartburn. Her 9 hour labor was not unusually strenuous. She was delivered easily with low Elliott forceps. Blood loss was estimated at 150 c.c. Inhalation anesthesia was administered but positive pressure was not used. During induction the patient vomited yellowish fluid, some of which she aspirated despite prompt pharyngeal suction. Laryngoscopy failed to reveal any trauma to the pharynx. On awakening from anesthesia the patient complained of difficult breathing and of a nonpleuritic, pressing, precordial pain. Examination revealed normal vital signs except for a pulse rate of 112. A faint, systolic, apical, adventitious sound was heard which was loudest during expiration. Expectoration of yellow material streaked with blood was observed. The abdomen and legs were normal. The fibrinogen level was 0.12 Gm. per cent (normal 0.2 to 0.6 Gm, per cent). Routine studies of blood and urine were unremarkable. An electrocardiogram revealed tachycardia and clockwise rotation. A chest x-ray (Fig. 1) confirmed the impression of aspiration pneumonia and also revealed air in the mediastinum. The next morning crepitus had appeared in the neck. The precordial sound was louder and could be heard both in systole and in early diastole. It was also present over the upper chest and neck and was presumed to represent Hamman's sign7 of mediastinal emphysema, since no pneumothorax was present. The patient was afebrile on therapy with antibiotics. The crunch varied in intensity from day to day and also changed with shifts of position. Râles appeared for several days at the right base where maximal aspiration had occurred. Only a minimal precordial crunch was audible at discharge 12 days after delivery. The x-ray showed disappearance of the pneumonia and marked subsidence of the pneumomediastinum (Fig. 2). Three weeks later only scarring in the right costophrenic angle remained.

#### Comment

It has been stated<sup>s</sup> that the sequence of vomiting, chest pain, and mediastinal emphysema demands thoracotomy with the presumptive diagnosis of

<sup>\*</sup>Present address: Capt. Robert P. Eisinger, 859th Medical Group, Bergstrom Air Force Base, Texas.

spontaneous rupture of the esophagus. Peptic esophagitis has been suggested as a predisposing factor and our patient's history of heartburn seemed consistent with such a condition. She did not go into shock, however, and no hydropneumothorax was demonstrable on upright films of the chest. Nevertheless a Lipiodol study was considered advisable to rule out the possibility of a leak from the esophagus into the mediastinum. Since no extravasation was noted either during fluoroscopy or on follow-up films we felt justified in pursuing a conservative course.

Gordon's series of cases of pneumomediastinum associated with delivery<sup>1</sup> revealed that the condition is most often seen in primiparas and in patients

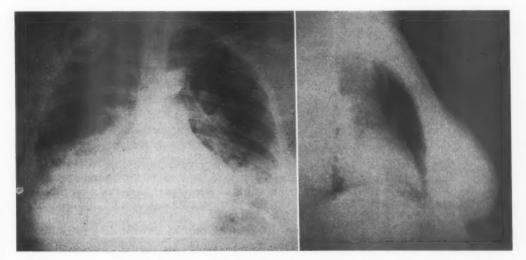


Fig. 1.—Frontal and lateral films of chest taken 4 hours after delivery. Pneumomediastinum and aspiration pneumonia are demonstrated.



Fig. 2.—Resolution of pneumonia and diminution in pneumomediastinum 10 days post partum.

with severe labors. Emphysema usually appears during the first stage of labor but has been reported several hours post partum. The condition is usually benign, but several deaths have occurred.

In normal respiration those alveoli which are most actively ventilated are most highly vascularized. When lobar collapse occurs the corresponding vascular supply is diminished. When, however, the alveoli of a given area are overinflated or the blood supply diminished, an imbalance is created between intra-alveolar and perivascular pressures. Air then leaks out into the perivascular spaces and dissects its way to the mediastinum and thence to the neck. As the Macklins have shown, no air dissects along the bronchi since endobronchial pressure is in equilibrium with alveolar pressure. When small areas of atelectasis occur, the adjacent areas of compensatory emphysema may be relatively undervascularized and distended. If, furthermore, air egress from these areas is prevented by inflammation or aspirated material in the bronchi and if the pores of Kohn do not offer access to normal alveoli, the stage is set for rupture of alveoli, interstitial pulmonary emphysema, and pneumomediastinum. Newborns with atelectasis and patients with pulmonary infections are therefore vulnerable. The importance of bronchial obstruction is emphasized by Clerf's observation10 that metallic foreign bodies very rarely cause interstitial emphysema probably because, although they have great tendency to perforate the bronchus, they rarely occlude it completely. Vegetable foreign bodies, however, are more commonly occlusive and more commonly cause interstitial emphysema.

Generalized overinflation of the lungs also predisposes to alveolar rupture. Thus, positive pressure anesthesia, resuscitation of the newborn, and bomb blasts may cause interstitial emphysema and pneumomediastinum. Aspiration of blood or fluid predisposes to pneumomediastinum by causing scattered areas of atelectasis with adjacent compensatory emphysema and at the same time stimulating coughing. The diagnosis of mediastinal and interstitial pulmonary emphysema must be considered in any dyspneic post-operative patient so that incision of the neck or trocar release of mediastinal air may be resorted to if needed.

If overinflation of alveoli may predispose to interstitial emphysema, a relative drop in the intravascular pressure in the lungs also may favor alveolar rupture into the vascular sheaths. Hence, congestive heart failure, bleeding with shock, pulmonary embolism, or pulmonary valvular stenosis or insufficiency may lower intravascular pressure by decreasing pulmonary blood flow. Forced expiration against a closed glottis reduces venous return to the right heart while increasing intra-alveolar pressure; indeed, Rosenblum and Silverman<sup>11</sup> describe a case in which an 18-year-old soldier induced mediastinal emphysema with the Valsalva maneuver with suicidal intent. A similar maneuver is executed in blowing the nose, heavy lifting, defecation, playing wind instruments, violent coughing, and parturation.

Macklin and Macklin<sup>9</sup> have pointed out that pneumomediastinum becomes dangerous when pressure of air bubbles on the healt and great vessels obstructs circulation, when air bubbles in the interstifial tissues of the lungs cause splinting and prevent respiration, when tension pneumothorax or bilateral pneumothorax occurs, when there is severe rulmonary inflammation, or when escape routes for the air into retroperitoreum and neck are not opened out. This latter point is confirmed by the work of Ballon and Francis, 12 who found that when mediastinal emphysema is greatest subcutaneous emphysema is usually slight. A preterminal patient may have no subcutaneous emphysema and then recover dramatically as air bursts into the neck, relieving the pulmonary and mediastinal "air block." Webb,

Johnston, and Geisler<sup>13</sup> have presented experimental evidence that the interstitial pulmonary emphysema splinting the lungs and compressing pulmonary vessels is essential for the production of symptoms. Their dogs with mediastinal emphysema alone did not show circulatory collapse.

Pneumomediastinum may mimic heart disease with dyspnea, cyanosis, chest pain, and falling blood pressure. Unfortunately, it may also be associated with myocardial infarction.<sup>14, 15</sup> Interstitial emphysema and pneumomediastinum may be unsuspected until they cause or contribute to death. If considered, the diagnosis can usually be made with a lateral roentgenogram which demonstrates air in the retrosternal space. The streaks of interstitial pulmonary emphysema can often be discerned on the frontal film if they are sought.

In our case the negative examination of the pharynx and the occurrence of the crunch the day before air appeared in the neck confirmed the impression that the air entered the tissues from the lower respiratory passages (esophageal perforation was not excluded by these observations but only by the benign course and the Lipiodol swallow). Perhaps some minimal amniotic fluid embolism occurred, as suggested by cardiac rotation and depression of blood fibringen. Further, the presence of aspiration presumably with local atelectasis, some blood loss, and the straining at labor contributed to an alveolar-vascular pressure differential and provided an ideal situation for the appearance of interstitial pulmonary emphysema and hence pneumomediastinum. It only seems surprising that similar cases are evidently so rare.

# Summary

A case of pneumomediastinum and aspiration pneumonia occurring as a complication of labor is presented. Spontaneous rupture of the esophagus had to be considered in the differential diagnosis. The mechanism of pneumomediastinum and its relation to interstitial pulmonary emphysema are discussed.

We are grateful to Drs. Harry and Morton Vesell for their encouragement and helpful interest.

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# METALLIC INTRAUTERINE FOREIGN BODY IN TERM PREGNANCY

Case Report

CARL L. ARMSTRONG, CAPTAIN, MC, AUSR, AND PAUL S. ANDRESON, COLONEL, MC, USA

(From the Obstetrical-Gynecological Service, Tripler United States Army Hospital, Honolulu, Hawaii)

INTRAUTERINE metallic foreign bodies compatible with full-term gestations have not been reported in the literature to our knowledge. Adair alluded to the presence of a retained pessary (substance not stated) found embedded in the placenta at the time of a term delivery. Batmen reported a case in which a rubber catheter had perforated a pregnant uterus, and after the catheter had been removed from the abdominal cavity the pregnancy went to term. Ellison reported a case in which a rubber eatheter was inserted into a pregnant uterus at 6 months gestation. This was passed spontaneously 4 to 5 weeks prior to term delivery of a viable 6% pound infant.

Veprovsky and Ostreich<sup>4</sup> reported 4 cases in which a rubber catheter used as an abortifacient had perforated the uterus in early pregnancy. Schockaert<sup>5</sup> presented a case in which a cotton tampon was found in a term uterus at the time of repeat cesarean section. Zakin<sup>6</sup> reviewed 7 cases of intra-abdominal foreign bodies (rubber catheters or pencils) which had perforated the uterus. The foreign body interrupted the pregnancy in each patient. Glavero Nunes<sup>7</sup> reported a case in which a primigravida had an obstructed labor due to a wooden spool embedded in the tissue of the cervical canal. After removal of the spool the patient was delivered uneventfully.

No reports have been found of metallic intrauterine foreign bodies compatible with full-term gestation. The following represents such a case.

A 29-year-old white woman, gravida iv, para iv, was first seen in the Gynecological Clinic on Dec. 9, 1955, two weeks after her first missed period, complaining of nausea, vomiting, frequency of urination, and general malaise. Her last normal menstrual period was Oct. 23, 1955. The patient stated that she had had a contraceptive "gold ring" inserted into the uterus in Japan following the birth of her last baby about five years before. There had been no difficulty during the time the patient used this ring. Examination showed a slight cervicitis with a scant bloody discharge, and a uterus consistent with early pregnancy. The estimated date of confinement was July 30, 1956. An x-ray of the pelvis (Fig. 1) showed the contraceptive device to be in the uterus, consisting of a coiled wire spring approximately 2.5 cm. in diameter to which was attached a smaller solid disc suspended from the outer ring by metallic ring attachments. No other abnormalities were noted radiographically.

On Dec. 20, 1955, the toad test was reported as positive, hemoglobin 7.3 Gm., erythrocyte count 2.3 million, and a corrected sedimentation rate of 6 mm. per hour. It was decided that no operative interference would be attempted. The patient was admitted to

the hospital on Dec. 21, 1955, and received 1,000 c.c. of whole blood. Her subsequent prenatal course was essentially uneventful, with a total weight gain of 17½ pounds.

An anteroposterior x-ray of the pelvis on March 13, 1956, showed the uterus to be enlarged to above the iliac crest with the fetal head discernible. The contraceptive device appeared to be at the internal os. An x-ray of the abdomen on July 17, 1956 (Fig. 2), showed a single near-term fetus, vertex presenting, with the ring visible superimposed over the fetal skull.

On Aug. 8, 1956, the patient was admitted to the hospital with regular uterine contractions and ruptured membranes. Temperature, pulse, respirations, and blood pressure

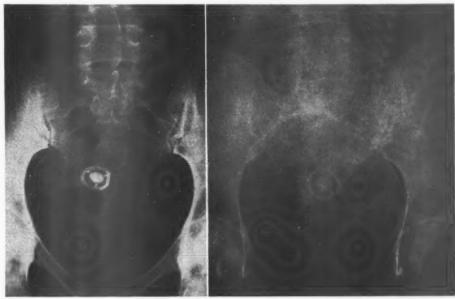


Fig. 1. Fig. 2.

Fig. 1.—Intrauterine contraceptive device with a 4 weeks' gestation.

Fig. 2.—Thirty-eight weeks' gestation with contraceptive device adjacent to fetal skull.



Fig. 3.-Portion of term placenta with contraceptive device attached to chorion.

were within normal limits. Physical examination was negative except for a gravid uterus containing a term-size fetus in vertex presentation. Rectal examination revealed complete effacement, 3 cm. of cervical dilatation, and the presenting part at station minus one. Two hours later, after a normal first stage of labor, the patient had a spontaneous delivery of a viable 6 pound, 101/2 ounce male infant in good condition. The placenta was delivered complete after a 49 minute third stage. While this was a prolonged third stage, there was no indication for manual removal of the placenta. An examination of the placenta showed the metallic device previously seen on x-ray to be attached to the chorion

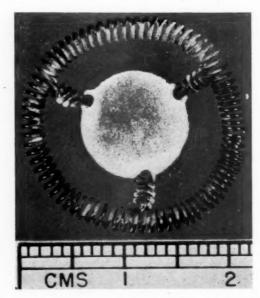


Fig. 4.-Metallic contraceptive device recovered from chorion.

near the point of exit of the infant (Figs. 3 and 4). The position of the foreign body was such that it would have been between the chorion and the uterine wall. A manual exploration of the uterine cavity suggested that the site of implantation of the placenta was on the anterior fundus. The postpartum course was completely uneventful and the patient was discharged on the third postpartum day.

# Summary and Conclusion

A term gestation coexistent with the presence of an intrauterine metallic foreign body has been presented. Several reports are reviewed in which nonmetallic foreign bodies were compatible with term gestations.

A foreign body complicating an intrauterine pregnancy per se is not an indication for interruption of pregnancy. The presence of a foreign body does not necessarily prevent pregnancy nor does it cause abortions in all cases.

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# DEPARTMENT OF CURRENT OPINION

Re-evaluation

# THE HISTOGENESIS OF ENDOMETRIOSIS

G. H. Gardner, M.D., R. R. Greene, M.D., and Brooks Ranney, M.D., Chicago, Ill.

IN 1953 we¹ surveyed the recent literature having to do with the histogenesis of endometriosis and gave short shrift to the widely accepted Sampson theory. This theory proposes that endometriosis is caused by retrograde flow of menstrual fluid out the tube with fragments of viable endometrium which implant and grow. We considered that the evidence for this theory was inadequate and more probably endometriosis arose in situ by a process of metaplasia from structures derived from the embryonic celom.

One of the main reasons for our doubting the Sampson theory was the fact that menstruation is caused by ischemic necrosis and subsequent slough. It seemed unlikely that these sloughed fragments would be viable and could implant and grow. Recently, however, Ridley and Edwards<sup>2</sup> performed an elegant experiment which convinces us that menstrual fluid may contain viable endometrial fragments. In brief, they injected menstrual endometrial debris into the anterior abdominal wall of patients upon whom they subsequently operated. In one patient they obtained definite endometriosis in the injection site. Granted that this is only one instance, but it certainly appears to be authentic. For this reason we must admit that menstrual fluid may contain viable endometrium and that endometriosis may result from retrograde menstrual flow. In other words, in some instance at least, the Sampson theory may be correct.

We are not willing to go whole hog on the matter. We do not believe that the Sampson theory can explain all instances of endometriosis. In fact, we do not know how often such a mechanism could be responsible for the causation of the ordinary garden variety of pelvic endometriosis. The facts still remain, however, that menstrual fluid may contain viable endometrium and that retrograde menstruation may be one of the causes of endometriosis.

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IN 1929 Graefenberg reported for the first time the celebrated ring which bears his name and which has subsequently been the center of great dispute among gynecologists all over the world. Graefenberg's motive was contraception, and he claimed for his device both safety and effectiveness.

However, the reception accorded this invention was from the start stormy in the extreme. At the seventh International Congress for Birth Control (1930), Pankow, Hammerschlag, Küster, Adler, and Frei all expressed opposition to this innovation—although not one of these distinguished gentlemen had ever had any experience of his own with the ring! On the other hand, Norman Haire of London, who had had experience with the ring, staunchly defended it.

Much of the opposition—to the dispassionate historian's view of today—apparently arose from the unfortunate experiences with the earlier intrauterine devices, such as Pust's pessary. The previous instruments, however, had included extensions which protruded

through the cervix into the vagina.

Nevertheless, the opposition won the day, at least in the United States. Thus the Greenhill and the Curtis texts mention the method only to condemn it. The Crossen volume does not even mention it. To all intents and purposes, this technique has disappeared in this country. Therefore, in seeking a re-evaluation of the Graefenberg ring, the Editors have turned to a foreign country, and Dr. W. Oppenheimer, Director of the Department of Gynecology and Obstetries at the Shaare Zedek Hospital in Jerusalem, has responded with this aecount of his experiences with this technique.

The Editors must perforce point out that the publication of this re-evaluation does not constitute an official or a personal endorsement on their parts of the Graefenberg ring as a contraceptive technique. We will not repeat the error of the first vehement critics, so, not having personal experience with the method, we must remain objective. We can speak neither for nor against it, and Dr. Oppenheimer is more

than able to speak persuasively for himself.

# PREVENTION OF PREGNANCY BY THE GRAEFENBERG RING METHOD

A Re-Evaluation After 28 Years' Experience

W. Oppenheimer, M.D., F.I.C.S., Jerusalem, Israel

(From the Department of Gynecology and Obstetrics, Shaare Zedek Hospital)

A T A time when so many countries are overpopulated, the prevention of pregnancy has become a consideration of increasing importance. The medical or eugenic indication for the interruption of pregnancy is recognized in many parts of Europe and America, while in Japan and India, for example,

it has become an official instrument of population policy. Since there is some danger in the interruption of pregnancy, a method of preventing pregnancy, which would be free from risk, has become a problem of the first order.

For the past 70 years, since Mensinga¹ introduced the "Dutch Cap," a soft vaginal rubber pessary with a spiral elastic rim, this pessary, with its several variants—such as Ramses, Matrisalus, and Diaphragma—has found general acceptance despite the fact that it has some disadvantages. The manipulation of introducing the cap shortly before intercourse hinders many women from experiencing orgasm and may lead to nervous disturbances. Moreover, in cases where the anterior vaginal wall has descended, as well as in cases of retroversion of the uterus, the method frequently fails. Its safety is approximately 95 per cent. The hard cervical caps, which were introduced during the twenties and then commonly used in Central Europe, have a great many ill effects—erosions, secretion retained in the cap which gives off offensive odor, and hypertrophy of the vaginal mucosa around the rim of the cap. These hard caps are therefore regarded as unsanitary. The "safe period" method has proved too uncertain. Under the circumstances it is understandable that there should be a universal search for a better and safer method to prevent pregnancy.

It is for that very reason, and because I believe the Graefenberg ring is an excellent method, which, while discussed in the overheated atmosphere of the early thirties, could not be considered objectively, that I am bringing up the question again. The ring in my own experience and in that of other reliable gynecologists has shown better results than any other method and has proved to be absolutely harmless. Nobody doubts that there is a possibility of infection, as in every intrauterine procedure, if one does not work with all the care and asepsis necessary.

Since 1930 I have inserted the Graefenberg ring 866 times. Since the beginning of writing this re-evaluation another 150 rings have been inserted. On the basis of my findings I consider it far superior to other preventive methods for the following reasons:

- 1. I have never, in more than 1,000 cases, seen any illness caused by it.
- 2. It yields far better results than the soft rubber caps.
- 3. It can be applied also (a) where the patient refuses the soft rubber cap for psychosexual reasons, (b) in cases of descensus of the anterior vaginal wall, and (c) in cases of retroflexion of the uterus.
  - 4. It is inserted by the physician only once in 12 months.
- 5. It does not cause sterility subsequent to its removal and patients can then become pregnant just as quickly as women who have never worn a ring.

During the first 2 to 3 years I used the Graefenberg silver ring and then switched over to the silkworm gut ring. I fasten a piece of silver wire to hang from the ring so that the presence of the ring can be ascertained by x-ray examination.

# Technique of the Method

The silkworm gut ring (which I shall call the silk ring) is usually inserted 3 to 4 days after the end of the menstrual period, and removed 9 to 12 months later, a day or 2 before the beginning of menstruation. Prior to the insertion of the ring the patient is carefully examined and swabs are taken from the cervix and urethra. Patients with any kind of inflammation and those with

suspected genital tuberculosis are excluded and so are patients with severe bleeding caused by submucous fibroma, endometriosis interna, and hyperplasia

glandularis evstica.

For the actual insertion of the ring all the instruments have to be sterilized. One needs, apart from the normal gynecological instruments, a special instrument to insert the ring which I shall describe below. The silk ring consists of 3 or 4 intertwined threads of silkworm gut each 14 cm. long with a knot at either end. In order to avoid any cracking of the silk threads while they are being intertwined, I soften them in warm water prior to knotting the ends and making the ring; this is to ensure that the end points or a cracked thread will not pierce the uterine wall. The silver wire attached to the ring should be 0.2 mm. thick. The instrument for inserting the ring is a thin hollow sound slightly bent at the upper end like a normal uterine sound; 0.5 cm. from its point the sound has a notch. The ring is fixed into this notch by means of a thin metal rod passing through the sound. In order to do this the ring is gripped by the anatomical forceps in such a manner that all the silk threads are placed one alongside the other so that the metal rod can pass over the threads and fix them into the notch of the sound (Fig. 1). After iodization of the cervix and vagina

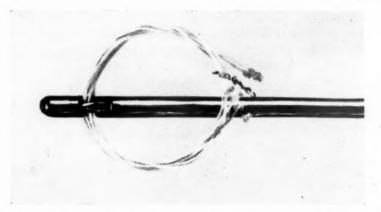


Fig. 1.—Part of the instrument for introducing the ring, showing the mechanism for fixing the ring.

and seizure of the cervix with the tenaculum forceps, the instrument carrying the ring is introduced into the uterine cavity like a uterine sound. Then the rod which passes through the instrument is withdrawn a few centimeters, thereby releasing the ring. The ring remains in the cavum uteri and the instrument is removed from the uterus slowly and carefully with slight rotatory movements. The whole process is practically painless and lasts only a few minutes; the actual insertion takes 3 to 4 seconds at the most.

The removal of the ring also takes only a few seconds. For this I use an instrument resembling a crochet hook but rounded at the top. After grasping the cervix with the tenaculum forceps the instrument is passed into the fundus uteri and when withdrawn it easily hooks onto the ring. I avoid removal and insertion—that is, changing the ring—in one session, in order to give the uterine mucosa a chance to rest for a few days.

#### **S**tatistics

During the years 1930-1957 I have equipped 329 women with 866 rings, effecting one to 20 insertions per case (Table I).

TABLE I

NO. OF CASES	NO. OF INSERTIONS	NO. OF CASES	NO. OF INSERTIONS
158	1	1	11
66	2	2	12
36	3	2	13
25	4	1	14
14	5	1	15
8	6	1	16
5	7	1	17
3	8	1	19
1	9	1	20
2	10		

# Advantages of the Method

The most outstanding quality of the ring method is its absolute harmlessness. In 866 insertions I have never seen any kind of inflammation or infection whatever, even in the presulfa and preantibiotic era. Moreover I have not had to use any antibiotic or sulfa preparation in any of the 866 insertions.

If earlier literature reports cases of all kinds of inflammation and even death then this may be accounted for in the following ways: (1) the method was not applied properly and aseptically; (2) the ring was inserted in cases of latent or unrecognized infection; (3) the patients were subsequently infected with gonorrhea or other disease; (4) upon failure or after the ring had dropped out, an illegal abortion had been earried out by an unpracticed or irresponsible person.

The second advantage of the method is its effectiveness. I have experienced 2 failures in 150 insertions of silver rings, i.e., 1.3 per cent; and 20 failures in all insertions, silver rings and silk rings, i.e., 2.4 per cent. But if we consider that the total of the 866 rings were in situ for an aggregate period of 793 years, i.e., 10,309 cycles, we arrive at one gravidity in 515 cycles or about 40 years. The rubber cap, on the other hand, shows 5 per cent failures; i.e., 5 failures in 100 cycles and 25 failures in about 40 years. The Graefenberg ring is thus 25 times as safe as the rubber cap. No other method offers such a high degree of safety. In a number of cases the ring has dropped out unnoticed. In 9 of my cases the ring was found in the vagina either by me during the follow-up examination or by the patient herself. In another 21 cases I found the end of one thread just visible in the os externum, i.e., the ring had slipped forward but was not yet outside the os and could be replaced by another ring in time to prevent conception. We know nothing definite as to what causes the ring to slip out of the uterine cavity. Possible causes are: (1) the ring is too large: (2) the uterus is too sensitive and therefore ejects the ring; (3) the internal os is too wide open and the ring therefore slips down gradually: (4) contraction of the uterus during orgasm leads to ejection of the ring; (5) the ring was left too long in water after sterilization and thereby became too soft so that during insertion it was compressed in the cervical canal and did not regain its original shape.

It is to be assumed that the silk ring is less liable to cause contractions than the silver ring, since of my 866 rings, approximately 700 of which were silk rings, only 5 per cent slipped forward as against 20 per cent of the silver rings inserted by Norman Haire and 17 per cent of those inserted by Leunbach.<sup>2</sup> Three years ago I changed the silk ring to a form similar to the silver ring by intertwining the threads 3 times instead of twice and by using 4 instead of 3 threads. Since that time no case of pregnancy or of dropping out or of slipping forward has occurred. In spite of that I would advise 2 to 3 control

examinations after insertion of the ring. Occasional failures are possible even when the ring is properly in position; in the few such cases observed by me, pregnancy and delivery were normal. In one of these cases an x-ray revealed the ring to be in utero 6 weeks after delivery and it was easily removed 2 months after confinement. In 2 of my cases where there was amenorrhea without pregnancy I checked the ring by x-ray and was thus able to reassure these patients. The patients continued to wear the ring and menstrual periods reappeared.

It is interesting to note that the ring does not become less efficacious by habitual wearing; on the contrary I have never observed a failure after the third or fourth insertion. On the other hand as soon as another pregnancy was desired it occurred spontaneously without any treatment and only a short time after removal of the ring. I have never had to treat for secondary sterility any ring-wearer who had become pregnant before without previous treatment.

I have given up using the ring in nulliparas for contraception because in such cases it is rejected more frequently than in parous women. I have found that after abdominal cesarean section, in cases where, except for a narrow edge, the os externum has expanded but has not visibly torn, the ring can easily be

inserted and keeps well in place.

Perforation during insertion of the ring appears to be very rare. The only case which I know of was reported by Murphy.<sup>3</sup> In this case there was a complete perforation of the lateral uterine wall and the silver ring was lodged in the right parametrium. The patient became pregnant and after x-ray had shown the ring to be outside the uterus, it was removed by laparotomy and the

pregnancy continued undisturbed.

In ring-wearers who became pregnant and had spontaneous abortions, Stefko frequently found deformities of the fetus and the placenta which he ascribed to the ring; but Mall<sup>5, 6, 7</sup> and Keibel and Mall<sup>8</sup> had already discovered 70 per cent of abnormalities of the ovum during the first month, and 50 per cent during the first and second months of pregnancy in cases of spontaneous abortion among patients who did not wear a ring. Hertig, Rock, 10 and their co-workers11, 12, 13 found in 1,000 cases of spontaneous abortion 61.7 per cent of abnormal ova, and hydatidiform degeneration of the chorionic villi in twothirds of these cases. Corner<sup>14</sup> found similar results in other mammals, especially in the pig. Stefko's view is also contradicted by my own experience and that of other writers; neither the babies who had been carried to term by ringwearers nor the respective placentas showed any deformity. Despite his interesting investigations, Stefko's conclusions have thus been completely dis-There is therefore no justification whatever for interrupting pregnancies occurring with the ring in situ for fear of fetal deformity. I have never observed extrauterine pregnancy as a consequence of the ring.

If we consider that in the presulfa and the prepenicillin era over 50 per cent of all gynecological diseases were of an inflammatory character and that more than 50 per cent of gynecological operations, at least in large Central European cities, were for the remedy of inflammatory diseases and their consequences, we can fully appreciate the remarkable harmlessness of a correctly performed insertion of the silk ring and what it means that in over 1,000 insertions I have never observed a resultant inflammation or extrauterine preg-

nanev.

Sterility after wearing the ring has not occurred in any of my cases. A great many women had the ring changed time after time for many years, and some, despite my warnings, wore the same ring for 2 to 4 years without any complications. In no case was treatment for sterility required in order to induce a pregnancy. In many cases pregnancy occurred in the first month after removal of the ring, in others after 2 to 4 months, and in 2 cases after

6 months. Many of my patients were the ring between several pregnancies, which always occurred spontaneously whenever desired. All pregnancies went to term.

In the early stages of wearing the ring the patients occasionally have increased and prolonged bleedings, very rarely also slight bleedings between the menstrual periods. Patients who have been warned against the method by a third party are especially prone to complain at first; however, these symptoms practically always disappear when the patient is given sufficient confidence. There is often a slight brownish discharge a day or two before and after the menses. It is important therefore to inform the patient about this fact prior to insertion. Removal of the ring because of increased bleeding is rarely necessary. I have done it in only 2 cases, in which the ring was introduced 8 weeks after confinement, when perhaps the uterus was not yet fully involuted.

It is interesting to note that sometimes the reverse happens; the menses are shortened and severe and lengthy menstruations become completely cured and normalized by the ring. This occurred in those cases in which the prolonged bleedings have a psychological basis.

All experience tends to disprove the allegation that the Graefenberg ring occasions tumors:

1. I have never observed cancer of the uterus (cervix or corpus) in any of the ring-wearers, although many of them have worn the ring for 10 to 20 years (one for 28 years). Theoretically, cancer of the uterus in wearers of the silk ring is as little to be expected as cancer of the stomach or intestines after an operation, involving the use of silk thread, on these organs.

2. Among my patients who had worn the ring there were only 2 cases of ovarian tumors, one a dermoid and the other a cystoma simplex; that is to say, the occurrence of ovarian tumors is not higher than in those who are not ring-wearers

3. There has been no endometriosis interna or externa following the use of the ring.

4. Myoma in ring-wearers has been observed by me in 7 cases. In one of them the patient had already had an operation with enucleation of multiple myomas a few years before the first ring had been inserted. She had later had a parametrically developed cervical myoma which in pregnancy blocked the entry of the fetal head into the pelvis minor so that she had to be delivered by cesarean section. Since then, although the patient started wearing the ring after that birth and has worn it now for several years, the fibroid has shrunk continually. This case therefore has to be deducted from the 7 myoma cases. The remaining 6 cases include several which, in all probability, were not caused by the intrauterine ring. In one of these cases I did not discover the fibroid until 6 years after the last ring had been removed. But even if we reckon 6 cases of myoma in 329 ring-wearers, this is a proportion definitely within normal limits.

So far, I have carried out 10 test curettages immediately upon removal of the ring. They were examined at the Pathological Institute of the Hebrew University and Hadassah Medical School, Jerusalem, and they showed no signs of endometritis or any other pathological changes. This agrees with the results of the examinations carried out by Robert Meyer and some British pathologists.

The cause of the effectiveness of the ring has not yet been established. We have to think of several possibilities. There might be the formation of a deciduoma which can be produced by mechanical, chemical and electrical methods. It was first produced by Loeb<sup>15</sup> in 1907 in experiments with guinea pigs and rabbits and later by other research workers<sup>16-25</sup> in other animals and

finally by Eichner<sup>26</sup> in human beings. It is interesting to note that a number of scientists pulled a loop of silk thread, as a mechanical stimulus, through the cavum uteri of the animal in order to produce a deciduoma without relating it to contraception, just as Graefenberg did in his contraceptive device without relating it to deciduoma.

In earlier literature it was suggested that the ring works by causing a change in the pH content in the uterine cavity, or, as Graefenberg maintained, by an early overdevelopment of the secretory phase of the uterine mucosa which might prevent the settling of the ovum. Norman Haire<sup>30</sup> on one occasion expressed the opinion that the ovum might settle on the ring itself, and, on another occasion, that the ring as such might produce increased alkalinity of the mucosa corporis which would kill the sperma and thus prevent pregnancy. Carleton,<sup>27</sup> in experimenting with rats, found atrophy of the uterine mucosa in the parts where the ring touched the uterine wall, and believed this to be the cause of This latter conjecture is very unlikely since the ring touches only a small sector of the uterine mucosa and the fertilized ovum has an opportunity of settling in many other places. I, myself, thought also that a trail of cervical mucous which became attached to the ring might remain after the introduction of the latter through the cervix, changing the alkalinity of the cavum. However, in a case where I amputated the uterus with the ring in situ, such a connection between the ring and the cervical mucous could not be observed. Another explanation, which occurred to Bloch, 28 Director of Research, Dead Sea Works, was that the ring might make slight rotatory provements in the cavum uteri and in doing so sweep the ovum out of the uteris. Whether the ring effects a change in the hormonal production is a further question. The work done by Pineus and co-workers29 could point in this direction. Examinations are still going on in different directions.

# Summary

- 1. For the prevention of pregnancy I use a variant of the wraefenberg ring, viz., a silkworm gut ring consisting of 3 or 4 threads to which a short piece of silver thread is fastened in order to ascertain at any time by k-ray whether or not the ring is still in place.
- 2. I have inserted a total of 866 rings in 329 patients, and a further 150 since the beginning of the writing of this paper. Some women have worn rings for more than 20 years—one patient for more than 27 years—the rings being changed every 9 to 12 months.
- 3. The method is absolutely harmless. In the course of 28 years of experience I have not observed a single inflammation of any kind whatever, even in the presulfa and prepenicillin era. Histological examinations of the uterine mucosa immediately upon removal of the ring have never shown any inflammatory or other pathological changes; the examination of the tissue formed on the ring merely showed signs of foreign body reaction such as are formed after operation and which result from silk threads which have been sewn in.
  - 4. I have in no case used sulfa preparations or antibiotics.
  - 5. The ring method proved to be 25 times as safe as the diaphragm method.
- 6. The insertion of the ring is practically painless and requires no anesthesia. After insertion the patient can immediately resume her usual occupation.

- 7. The silver ring with its 1.3 per cent failures proved safer than the silkworm gut ring in its original form (2.4 per cent failures). In spite of that I have given up the silver ring for reasons mentioned in this paper. In recent years since I have formed the ring of 4 instead of 3 silkworm gut threads, and intertwined them thrice instead of twice, there have been no failures at all. In view of the fact that before that change, in about 5 per cent of the cases, the ring slipped out of place, I would recommend regular examinations in order to discover this in time for the ring to be removed and a new one inserted before conception occurs.
- 8. No miscarriage occurred in those cases where pregnancy took place while the ring was in situ. No malformation of the fetus or placenta was seen in these cases. No cases of sterility have occurred after removal of the ring. All women who wished to become pregnant became so spontaneously without any treatment, generally within one to 4 months and in 2 cases within 6 months.
- 9. In 28 years of experience I have not seen a single case of carcinoma of the cervix or the corpus in ring-wearers.
- 10. Ovarian tumors and fibroids among ring-wearers were not more frequent than in other healthy women; I observed, among 329 women, 2 benign ovarian tumors and 6 fibroids, some of which appeared only several years after removal of the ring.
  - 11. No endometriosis occurred.
  - 12. No extrauterine gravidity occurred as a consequence of the ring.
- 13. Increased and prolonged bleedings occur sometimes in the early stages of wearing the ring, but usually disappear within 2 to 3 months. There is usually a slight brownish secretion one or 2 days before and after menstruation. In some cases, on the other hand, I have observed a shortening of prolonged menstrual bleedings, probably for psychological reasons.
- 14. In some women menstruation which previously had occurred only every  $2\frac{1}{2}$  to 3 months became perfectly normal while they wore the ring.
- 15. In hypoplasia of the uterus the ring may stimulate growth. In one severe case I have seen gravidity after years of sterility. Further experience in this field is necessary.
- 16. I had to remove the ring in only 2 of my cases; in one of them because of heavy menstrual bleeding and in the other because of recurrent slight intermenstrual bleedings. In both cases, the ring had been introduced about 8 weeks post partum. Although cases of this kind account for less than 0.25 per cent of the total, I recommend that the ring should not be inserted until 3 months post partum. For the majority of eases 2 months post partum is sufficient.
- 17. The cause of the effectiveness is not known. Different possibilities are discussed in this paper; investigations are still being pursued in various directions.

I would like to thank Professor Unger for the pathological examination of the curettage material and the tissue adhering to the ring.

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# Reviews and Abstracts EDITED BY LOUIS M. HELLMAN, M.D.

# REVIEWS OF NEW BOOKS

Human Parturition, Normal and Abnormal Labor. By Norman F. Miller, T. N. Evans, and R. L. Haas. 248 pages, 66 figures. Baltimore, 1958, Williams & Wilkins Company. \$7.50.

Drs. Miller, Evans, and Haas have presented a basic, simplified, and well-categorized book for the practicing obstetrician and working resident. The entire subject matter is handled in the Harvard Outline Method and a quick glance will immediately bring to mind the skeleton structure on which the practitioner can build his case.

The language is simple and only the major problems receive attention. All the philosophy, theory, and background material are left to the standard references and the years of experience.

Obstetric and Gynecologic Milestones—Essays in Eponymy. By Harold Speert. 700 pages, 79 figures. New York, 1958, The Macmillan Co. \$15.00.

No true understanding of the present can be achieved unless man knows and understands his past and is cognizant of his continuity with it.

Essays in Eponymy offers a unique and fresh glimpse of our obstetric and gynecologic past. A man's name becomes attached to an organ, sign, instrument, or operation either because the discovery itself is of importance or, more frequently, because of the colorful character of the man. Speert has taken advantage of these facts to study the history of selected gynecologic and obstetric eponyms from the standpoint of both the scientific fact and the character and color of the man. These are presented with a brief description of the facts surrounding the scientific presentation and a brief abstract of the paper which evoked the eponym. In each case there then follows a picture of the man with a short biographical sketch. A list of pertinent references is usually appended.

To say that these essays are well done is to be guilty of gross understatement. Particularly, the biographical sketches are gems. They are executed in brief, bold strokes giving the character of the man and his time with the clarity of a photograph. In particular, interesting light is shed on points of controversy as in the case of the divided departments at Hopkins and the DeLee-Hillis quarrel.

Only one who has himself searched for some of these obscure items can appreciate the work, care, and persistence that went into this volume. For example, where does one find a picture of Stroganov? At the USSR Ministry of Health, of course, but even the Soviet Consul didn't know this, for we tried to find this picture a few months ago. Finding Brenner,

a general practitioner in a small African town, and then following him to Johannesburg only to discover through correspondence that he knew nothing of the fame of his "small research in gynecologic pathology" is exciting business. One is delightfully repaid even reading of this historic find.

This is excellent history and is thoroughly readable. Selection, in general, is good although why the Bracht maneuver is included in this company is not understandable. There is information here that is worthwhile and would be hard to come by elsewhere.

Gynecologic Radiography, Including Radiography of the Breast. By Jean Dalsace and J. Garcia-Caldéron. 188 pages, 360 radiographs, 2 tables. New York, 1959, Paul B. Hoeber, Inc. \$8.00.

The first atlas of gynecologic radiography is made available to American readers by Drs. Dalsace and Garcia-Caldéron. The authors have had extensive experience in the use of contrast media to augment the diagnostic value of gynecologic radiography and their interpretations have been amplified by clinical and anatomical findings. The translation from the French, by Dr. Hans Lehfeldt, has undoubtedly been a difficult task, but his efforts will be appreciated by those of us who wish to have such a reference manual as a guide for proper interpretation of hysterosalpingograms. Although a bibliography is absent, one cannot help but agree that a substantial list of reference material would add little to the value of the book.

The x-ray reproductions are clear and definite but the admixture of positive and negative x-ray prints is often very confusing, particularly because in this country most workers base their studies on the negative films. The authors discuss the relative merits of water-soluble and oily media, making a plea for the use of the former in sterility studies wherever there may be tubal stenosis, and also where it is desirable to demonstrate details of the mucous membrane. The comments concerning each of the radiographs are concise and clear and are often amplified by photographs of surgical specimens.

Uterine perforations and vascular and lymphatic injections, rare phenomena, are very vividly demonstrated as are the intrauterine synechiae.

The section on radiography of the breast is written by Charles-M. Gros and Robert Sigrist, and their use of charts and illustrations clarifies considerably the diagnosis of benign and malignant diseases of the breast by simple radiography and by contrast medium injection into the mammary ducts.

Callander's Surgical Anatomy. By Barry J. Anson and Walter G. Maddock, 4th edition. 1,157 pages, 1,047 illustrations. Philadelphia, 1958, W. B. Saunders Company. \$21.00.

A new edition of a standard authoritative work carries on the fine tradition of its predecessors.

The contents is divided into 12 parts ranging from the head to the lower extremities. In each chapter the basic anatomic facts are presented. The statistical anatomic norm as well as congenital and acquired variations are discussed and depicted. At the conclusion of each section the pertinent surgical considerations are reviewed and the general principles of the common operative procedures are described.

The chapters on the abdomen and on pelvic anatomy are extensive. The pelvis is divided into the traditional male and female types. No mention is made of either the Thoms or the Caldwell-Moloy classification. While attention is focused on congenital anomalies, no space is given to a discussion of hermaphroditism.

The print is large and clear and the text is profusely illustrated.

Sex and the Adolescent. By Maxine Davis. 317 pages. New York, 1958, Dial Press. \$5.00.

Sex in conversation as well as in literature has developed in our country from a strictly forbidden taboo to a topic of exaggerated and malformed proportions. Similarly,

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adolescence itself, once regarded as a mere stage of human development taken non-chalantly for granted by both parents and youngsters, has now become the focus of psychologists, parents, civic organizations, and practically everyone in the community. Adults virtually fear children in this stage of life—they are wary to mention certain topics to them; afraid either to place too many restrictions on them or let them have too much freedom; and, in general, treat them as kind of abnormal entities, not knowing what to tell them or not to tell them, or quite how to treat them. The unfortunate adolescent, therefore, is all too often left in a state of utter confusion, especially regarding the most important subject of sex—its emotions and ensuing actions. His parents tell him one thing, his friends another, and literature, movies, etc., something entirely different. Which is he to believe? And how, from this gathering of bits of information from here and there, can he obtain a clear reliable picture?

Basically, all he wants to know and understand is what is happening to himself, both physically and emotionally, and with what actions he should try to cope with his new body growths and inner feelings. Likewise, his parents' prime concern is what actions they should make to constructively and healthfully aid him in his stage of development. For both adolescents and parents then, Maxine Davis' book, Sex and the Adolescent, is a welcome and much-needed solution.

In this work, no subject is slighted, "hedged-around," or obscured by either overly scientific or sentimental explanations. The author discusses in a frank, nontechnical manner both physical and emotional growth and resulting actions, incorporating the most recent scientific findings with answers to quandaries and questions compiled from adolescents themselves. The result is a work extremely beneficial to parents for answering questions and guiding behavior, but most especially to the adolescent himself. In reading this he can understand his growth and development as well as that of the opposite sex and the relationships of both sexes in dating, courtship, and engagement. All of this is afforded him in a clear-cut, frank, and interesting style, explaining the old superstitions and falsities, which he may have gleaned from his peers or even adults, and giving him the forthright, down-to-earth, honest answers he desires in a manner for which he is likewise striving at this time—to be treated as an adult!

Clinical Endocrinology. By K. E. Paschkis, A. E. Rakoff, and A. Cantarow, 2nd edition. 941 pages, 274 illustrations. New York, 1958, Paul B. Hoeber, Inc. \$18.00.

A second edition of *Clinical Endocrinology* is as worthy of favorable comment as was the first edition. Many changes have been made in an effort to bring the material up-to-date. These changes have necessitated the rewriting of many sections.

The format is the same. There are 12 sections; 9 dealing with separate endocrine glands; one with obesity; one with endocrinology of pregnancy, and the last section with diagnostic procedures and the present commercial hormone preparations. The last section is one of the most informative parts of the text and a most valuable reference for diagnostic methods.

Each endocrine gland is discussed as to its embryology, anatomy, and physiology, which makes a valuable background for understanding the abnormal states.

Endocrinology is a rapidly changing science but this textbook contains most of the presently accepted viewpoints. The material is presented in a readable and logical manner which lends to easy understanding.

The bibliographies at the end of each section are quite complete for those interested in further investigation.

Obstetrical Practice. By Alfred C. Beck and Alexander H. Rosenthal, 7th edition. 1,115 pages. Baltimore, 1958, The Williams & Wilkins Co. \$14.00.

Since Obstetrical Practice first appeared in 1935 it has been one of the leading standard American textbooks. The work has always been popular with undergraduate students as well

as with obstetricians because of its straightforward, conservative approach and its many clear and simple illustrations. Many of the drawings were made by the senior author.

Fully cognizant of the striking changes which have taken place in the practice of obstetrics in the past few years the authors have thoroughly revised or rewritten many of the chapters. The chapters on the development, structure, and function of the placenta have been rewritten. The use of the abdominal binder has been deleted. The true Credé and the modified Credé procedure have been omitted and the Brandt-Andrews method substituted. The more frequent use of manual removal of the placenta is recommended. The tendency to use cesarean section for prolapse of the cord is noted.

Manual dilatation of the cervix, vaginal cesarean section, and the Spinelli operation for inversion of the uterus might well be omitted. The proper name on page 962 should

be Das, not Dask.

The portraits of the masters of the art, although badly reproduced, and the historical notes are pleasing features. The book remains one of the best of the hardy perennials in the garden of obstetric literature.

Occipitoposterior Positions. By Edward L. King. 106 pages, 60 figures. Springfield, 1957, Charles C Thomas. \$3.75.

This monograph is a concise summary of the author's extensive clinical experience with occipitoposterior positions. The etiology and diagnosis of this obstetric situation are discussed clearly and the suggested management of labors in such cases is conservative and logical.

About half of the book is devoted to a detailed description of the surgical and nonsurgical techniques used in the delivery of the persistent occipitoposterior presentation. This includes the indications and use of the various types of instruments including the Kielland and Barton forceps. There is an interesting historical note on the Scanzoni maneuver in addition to a clear description of this technique.

This is an easily read summary of the problems which occur in the management of occipitoposterior positions and should provide a good review for all who may be interested.

A Symposium on Non-Toxaemic Hypertension in Pregnancy. Edited by N. F. Morris and J. C. McClure Brown. 243 pages, 78 illustrations. Boston, 1958, Little, Brown & Company. \$8.50.

Among the 55 participants (45 from the British Isles) were 9 internists, 4 patholo-

gists, a neuropathologist, a psychiatrist, a pediatrician, and a geneticist.

The first 42 pages are dominated by the internists, pathologists, and the geneticist (speaking as a biostatistician). Here, some of the fundamental features of blood pressure maintenance and anatomic lesions of hypertension are discussed. The next 57 pages are given to the course of pregnancy complicated by essential hypertension, and this is followed by 35 pages in which secondary hypertensions are considered in relation to pregnancy. The management of pregnancy complicated by hypertension occupies about 50 pages and the remote prognosis is discussed in the fifth portion of the symposium.

The standards for the diagnosis of hypertension, used by different participants, varied from 120/70 to 140/90. The internists regarded such blood pressures, in nonpregnant subjects, as normal or without immediate significance. However, the obstetricians established that "trivial" hypertension does bode ill for some pregnant women. While a discussion of pre-eclampsia was not on the agenda, it did crop up here and there.

Although few new data are presented, the symposium is well worth study.

Textbook of Surgery. By H. Fred Moseley. 1,336 pages, 738 figures, 108 colored plates. St. Louis, 1959, The C. V. Mosby Co. \$17.00.

In this third edition of Textbook of Surgery, Dr. H. Fred Moseley has been able to fuse the contributions of numerous specialists into a single, readable, and most interesting volume. The book is introduced by a very stimulating chapter on the evolution of modern

surgery. Thereafter, such fundamental aspects of surgery as bacteriology, anesthesia, surgical technique, and preoperative and postoperative care are thoroughly presented and discussed. The main sections of the text are concerned with the various systems and areas of the body. Although no attempt is made to illustrate all the various surgical techniques and procedures, many of the fundamental concepts are well illustrated with colored plates as well as halftone prints. Only a very small section is devoted to gynecology; yet, most of the highlights are covered. As happens in all textbooks, current advances in therapy are too recent to be included. As an example, there is no reference in the discussion of choriocarcinoma to the spectacular results associated with chemotherapy; but such omissions are understandable. One small error was noted in the description of the staging of cancer of the cervix. The author states that a lesion involving the uterine corpus falls into Stage II. According to the international staging of cancer of the cervix, such a lesion is now called Stage I. Although one could probably cite several other minor discrepancies in other areas, the over-all tenor of the third edition of Moseley's Textbook of Surgery is most comprehensive and accurate. The bibliographies associated with each section contain a listing of films available on the subject matter including the source of the film. This in itself is a valuable asset to this excellent reference book.

#### Le Placenta humain, aspects morphologiques et fonctionnels. By Professor Jean Snoeck. 718 pages, 175 figures, 48 charts. Paris, 1958, Masson et Cie. \$25.00.

An extremely important publication, Le Placenta humain was brought to this reviewer's notice about 6 months ago. Since then his copy has been often read and frequently borrowed until it appears somewhat dog-eared.

It is a difficult and unrewarding task to attempt to assemble current information about even one aspect of the human placenta, not to mention any comprehensive data on the whole. In this paper-bound volume of 718 pages, Professor Snoeck has accomplished just this. The medical team of the Gynecologic and Obstetric Clinic of the University Hospital, St. Pierre, Brussels, under his direction, have included the results of their own multidisciplinary studies with a comprehensible synthesis of current research on human placentology.

The work is divided into 2 sections, Morphology and Physiology; the index is accurate and complete.

The original contributions presented in the volume are as follows:

- 1. Introductory study of placental histometry by means of a mechanical stage with an integrating micrometer.
  - 2. Study of placental glycogen by the frozen section technique.
  - 3. Study of the macroscopic characteristics of 350 placentas of known age.
- 4. Quantitative study of the evolution of the exchange membrane surface of the human placenta during pregnancy.
  - 5. Study of the passage of sucrose across the placenta.
  - 6. Estrogen secretion of the human syncytiotrophoblast in culture.
- 7. Identification of progesterone in human placental tissue by means of paper chromatography.
- 8. Identification of corticoids in human placental tissue by means of paper chromatography.
  - 9. Determination of the concentration of chorionic hormones in human placental tissue.
- 10. Quantitative and qualitative analysis of a corticotropic factor in human placental tissue.

Particularly outstanding are the chapter on permeability by P. Wilkin and the chapter on endocrine function by P. Rosa.

The original studies are skillfully interwoven with current knowledge and researches of others into a readable integrated whole. The photomicrographs are clear and well reproduced as are the rest of the figures. The paper is good and the format attractive. For this particular paperback the price is not high.

#### BOOKS RECEIVED FOR REVIEW

- Breast Cancer (Factors Modifying Prognosis). By A. J. Delario. 208 pages, 137 tables. New York, 1959, The Macmillan Co. \$7.50.
- Childbearing Before and After Thirty-five. By Adrien Bleyer, 1st edition. 119 pages, 17 tables, 10 charts. New York, 1958, Vantage Press. \$2.95.
- Current Therapy—1959. Edited by Howard F. Conn. 780 pages, 13 tables. Philadelphia, 1959, W. B. Saunders Co. \$12.00.
- Een Onderzoek Over Het Vaatstelsel Van De Placenta. By N. F. Th. Arts. 148 pages, 38 figures. Nijmegen, 1958. Promotor: Prof. G. P. M. Horsten.
- Groves' Synopsis of Surgery. Edited by Sir Cecil Wakeley, 15th edition. 650 pages, 190 figures, 13 plates. Baltimore, 1958, Williams & Wilkins Co. \$8.50.
- Lehrbuch der Geburtshilfe. By Heinrich Martius. 731 pages, 768 illustrations. Stuttgart, 1959, Georg Thieme Verlag. \$14.20.
- Maternity—a Guide to Prospective Motherhood. By Frederick W. Goodrich, Jr. 130 pages, illustrated. New York, 1959, Prentice-Hall, Inc. \$1.75.
- Physiotherapy in Obstetrics and Gynaecology (Including Education for Childbirth). By Helen Heardman, revised by Maria Ebner, 2nd edition. 244 pages, 94 figures, 7 tables. Baltimore, 1959, Williams & Wilkins Co. \$5.00.
- Practical Obstetric Problems. By Ian Donald, 2nd edition. 712 pages, 104 figures, 3 tables. Chicago, 1959, Year Book Publishers, Inc. \$11.00.
- Thank You, Dr. Lamaze. By Marjorie Karmel. 190 pages, 21 illustrations. Philadelphia, 1959, J. B. Lippincott Company. \$2.95.
- Therapeutic Radiology. By William Moss. 403 pages, 146 illustrations. St. Louis, 1959, The C. V. Mosby Co. \$12.50.
- Tumours of the Bladder—Neoplastic Disease at Various Sites. Edited by David M. Wallace, Volume 2. 352 pages, 202 figures, 35 tables. Baltimore, 1959, Williams & Wilkins Co. \$11.50.
- Urology in Outline. By T. L. Chapman. 176 pages. Baltimore, 1959, Williams & Wilkins Co. \$6.75.

#### SELECTED ABSTRACTS

#### Anesthesiology

Vol. 19, November-December, 1958.

\*Feldman, Stanley A., Forgaard, Dean M., and Morris, Lucien E.: Compatibility of a Synthetic Oxytocin (Syntocinon) With Anesthesia in Dogs, p. 787.

Peldman, Forgaard, and Morris: Compatibility of a Synthetic Oxytocin (Syntocinon) with Anesthesia, p. 787.

Syntocinon, a chemically pure oxytocic, in a dose of 1 unit per kilogram was investigated as to its compatibility with cyclopropane, trichlorethylene, and a barbiturate in dogs. No electrocardiographic abnormalities were detected with cyclopropane; the blood pressure varied in 15 experiments. Exaggerated sinus arrhythmia was observed in one of 3 animals during trichlorethylene anesthesia; the blood pressure rose in each animal. During barbiturate anesthesia an increase in blood pressure occurred in 2 instances; no change was recorded in the third dog. Syntocinon appeared to afford some protection against epinephine-induced arrhythmias under cyclopropane and trichlorethylene anesthesia.

H. Johnson

#### Fertility and Sterility

Vol. 9, November-December, 1958.

- \*Mastroianni, L., Winternitz, W. W., and Lowi, N. P.: In Vitro Metabolism of the Human Endosalpinx: Some Preliminary Studies, p. 500.
- \*Plate, W. P.: The Pathologic Anatomy of the Stein-Leventhal Syndrome, p. 545.
- \*Hassler, F. S.: Liothyronine Therapy in Female Infertility, p. 555.
- \*Taymor, M. L., and Selenkow, H. A.: Clinical Experience With L-triiodothyronine in Male Infertility, p. 560.

Mastroianni, Winternitz, and Lowi: The in Vitro Metabolism of the Human Endosalpinx: Some Preliminary Studies, p. 500.

A total of 38 fresh specimens of Fallopian tube were removed from patients with normal mentrual histories who were being subjected to hysterectomy for nontubal disease of the genital tract. Immediately after excision the tubes were placed in chilled isotonic saline and transported to the laboratory in an ice bath. The serosa and muscularis were incised longitudinally and stripped from the specimen along a clearly defined plane of cleavage. The remaining tissue surrounding the lumen, composed mainly of mucosa, and designated as endosalpinx, was left for study. A representative sample of each specimen was prepared for histologic examination to rule out intrinsic disease. The endosalpinx was supported by pith and sectioned transversely for study in the Warburg apparatus. Oxygen utilization was determined aerobically at 37° C. in Krebs-Ringer phosphate solution alone and with various added substrates. Observations were made during a 2 hour period.

Tissue survival was unaffected by the conditions of the study. The rate of oxygen uptake in various media remained constant through the second hour. In those instances where data were available for both tubes in a given patient, there was a similar rate of

<sup>\*</sup>This article has been abstracted.

oxygen utilization in each oviduct. When segments of specimens were studied separately, there was no appreciable difference in oxygen uptake between the fimbria and the outer or middle third of the endosalpinx. Slightly diminished activity was observed for the inner third. No significant variation in the oxygen uptake of the endosalpinx during the menstrual cycle was noted. Succinate caused an increased oxygen utilization whereas fructose produce no effect. Glucose, on the other hand, consistently depressed the uptake of oxygen, two thirds of the glucose being converted to lactate. It was concluded, therefore, that even in the presence of oxygen, there is a preference on the part of the endosalpinx for the aerobic pathway of glycolysis ending in lactic acid.

PAUL T. TOPKINS

#### Plate: Pathologic Anatomy of the Stein-Leventhal Syndrome, p. 545.

After reviewing the literature on the "polycystic ovary syndrome," the author describes, with the aid of pictures, the pathologic changes and tries to correlate them with the clinical findings. He then presents his clinical results following wedge resection of the ovaries.

The enlarged ovaries of the Stein-Leventhal syndrome are smooth, glossy, and gray, with no visible ovulation scars. It is often possible to demonstrate thickening of the tunica albuginea, under which are found a large number of primordial follicles. The cysts are follicular in type and variable in size. The layer of granulosa cells in these cysts is usually thin, which accentuates the hypertrophic luteinized theca interna. The theca externa is also luteinized at times. Some observers have even identified various collections of luteinized cells in the ovarian stroma. Sometimes a striking fibrosis of the ovarian stroma is found.

The author regards hirsutism as an expression of early virilization. He reasons that inasmuch as the 17-ketosteroid excretion is normal or only slightly increased, it is probable that the hormone responsible for the hirsutism must be different from the other androgens, or perhaps that it is possible that the substance is not excreted as a 17-ketosteroid. It is possible, moreover, for the hirsutism to result from a change in the estrogen-androgen balance. Hirsutism may therefore be present even with diminished 17-ketosteroid excretion provided the estrogen level is diminished considerably.

The origin of the polycystic ovarian changes is discussed. It is noted that similar changes are also found in regularly menstruating women who have borne children. Experimental evidence shows that the thickened tunica albuginea does not prevent ovulation. If it is of hormonal origin, ovulation is not prevented by a diminution of LH factor because the hyperthecosis is an expression of excessive LH production. When ovulation is suppressed the anterior pituitary increases its production of LH in an effort to force ovulation. Such overproduction of LH stimulates the theca interna, giving rise to hyperthecosis. In addition, an increased quantity of androgens is liberated, giving rise to hirsutism. If ovulation is impeded for a sufficiently long time hyperthecosis must eventually occur if the hypophysis is capable of increased LH production. Thus, a high gonadotropic level is a result rather than a cause of the cystic ovaries. If luteotropic hormone is also produced, the luteinized theca interna will be capable of producing progesterone, which may produce a secretory endometrium. Therefore the presence of a secretory endometrium is not conclusive evidence of ovulation.

During the period 1949-1956 the author performed ovarian wedge resection in 98 patients, the majority of whom showed the Stein-Leventhal syndrome. In 88 ovaries with hyperthecosis an attempt was made to establish a correlation between thickening of the tunica albuginea and the degree of hyperthecosis. The findings seemed to suggest that ovaries without hyperthecosis were more frequently found in the absence than in the presence of a thickened tunica albuginea. Ovarian hyperthecosis was present in 68 (83 per cent) and absent in 14 (17 per cent) of 82 anovulatory patients who were subjected to resection of the ovaries. Of 65 anovulatory patients showing ovarian hyperthecosis there were 37 who had normal ovulatory cycles after ovarian resection (57 per cent). On

the other hand, only 4 out of 14 patients without hyperthecosis (29 per cent) showed a favorable response after operation. This suggests that the results of ovarian resection are more favorable in the cases with hyperthecosis. Of 34 married women with hyperthecosis, 11 became pregnant after wedge resection of the ovaries (32 per cent). None of 7 married women without hyperthecosis became pregnant after operation. However, the author concludes that his series of wedge resections is too small to warrant the conclusion that the operation can be expected to yield good results in the presence of hyperthecosis.

PAUL T. TOPKINS

#### Hassler: Lyothyronine Therapy in Female Infertility, p. 555.

This study concerns 38 infertility patients who had been under the author's care for an average of 3.5 years. Every patient had a history of chronic fatigue or lethargy, dry hair or skin, or other symptoms of hypometabolism. Two of the patients were anovulatory while the others showed abnormal menstrual or ovulatory patterns according to basal temperatures, endometrial biopsies, or vaginal smears.

Therapy with liothyronine (Cytomel) tablets was started with 10 or 25 meg, daily and raised gradually to a level of 25 or 50 meg, daily for the majority of patients. All patients received therapy for at least one month and all but one of the patients who became pregnant continued medication until term. No other medication was given.

Definite improvement was demonstrated in 24 women treated with liothyronine (63.2 per cent). In 14 patients pregnancy supervened; in the others menstruation and ovulation were normalized. These patients also noted such improvement as oilier hair and skin, or they felt more alert and energetic than they did prior to therapy. Of the 14 pregnancies, 7 occurred after one mouth of treatment, the others after 2 to 6 months. Ten women delivered normal babies, 2 miscarried, and 2 are still pregnant.

No untoward effects of the medication were noted after adjustment of dosages of liothyronine. In order to establish the optimal dosage, however, medication was given in increasing amounts until mild nervousness, restlessness, irritability, or insomnia appeared. In all instances these symptoms disappeared when the dosage was reduced by 5 or 10 mcg. daily. The author concludes that liothyronine seems to be an effective drug for improving female fertility, even among women who have no obvious thyroidal disorders.

PAUL T. TOPKINS

#### Taymor and Selenkow: Clinical Experience With L-triiodothyronine in Male Infertility, p. 560.

A total of 28 infertile male patients were treated with an initial dose of 50 meg. of L-triiodothyronine (Cytomel) daily. The dosage of the drug was changed periodically in order to increase the basal metabolic rate to -5 per cent or higher. The daily range in the study varied from 50 to 125 meg., although one patient received only 25 meg. daily. The ultimate daily dosage was determined by the amount necessary to induce a measurable physiologic response either in the basal metabolic rate or in the characteristics of the semen. No untoward effects of the drug were exhibited by the patients, either during therapy or after discontinuation of therapy.

A sperm count of 40 million per cubic centimeter was arbitrarily selected as the lower limit of normal fertility. In addition, motility was considered to be normal only if, at the end of 2 hours, at least 60 per cent were motile and, at the end of 6 hours, at least 35 per cent. All semen specimens were obtained after 5 days of abstinence from intercourse.

For the purposes of presentation the 28 patients in the study were divided into 3 groups: (1) hypometabolic patients (BMR -10 per cent or less) with normal sperm concentration but with poor sperm motility; (2) hypometabolic patients with abnormal sperm counts and poor motility; (3) normal patients with deficiences in sperm count, motility or both.

In the first group there were 14 patients. In 8 patients 50 to 75 mcg. daily were required in order to achieve the desired therapeutic effect. Treatment was maintained from 7 to 32 weeks before the final specimens were obtained for analyses. In 10 of the 14 patients the results showed a significant improvement in 6 hour motility studies. In addition, in 7 of these 10 patients there was a marked increase in sperm concentration. Two patients not only failed to show improvement in sperm characteristics but in fact exhibited a decrease in 6 hour sperm motility studies.

In the second group the 6 patients were treated in a similar manner. Nevertheless, no improvement was noted in either sperm motility or concentration.

In the third group treated in this fashion, with a daily dose of 50 to 150 mcg. over a course of from 11 to 26 weeks, there was no improvement in 4 of the 8 patients. An improvement in 6 hour motility beyond the 35 per cent accepted as normal occurred in only 1 instance.

The authors conclude that L-triiodothyronine is of definite but limited value in the treatment of male infertility. The hormone, when given in relatively large doses, is of value in improving sperm motility and longevity only in instances where the initial sperm concentration is normal and where there is some evidence of hypometabolism. On the other hand, the study suggests that the indiscriminate use of this hormone in an effort to correct oligospermia is not warranted.

PAUL T. TOPKINS

#### The Practitioner

Vol. 182, March, 1959.

Neale, A. V.: Cerebral Palsy, p. 320.

#### Southern Medical Journal

Vol. 52, March, 1959.

Weed, J. C., and Barraza, D. F.: Management of Ovarian Carcinoma in 123 Patients
With Particular Emphasis on the Prophylactic Use of Radioactive Gold, p. 278.
Burke, H. A., and Liddle, G. W.: Endocrine Clinic—Virilizing Adrenal Hyperplasia, p. 283.

#### Wiener klinische Wochenschrift

Vol. 38, Aug. 22, 1958.

\*Cekon, Fritz, and Ehrlich, Hedwig: Contribution to the Question of Corpus Luteum Hormone and 17-Ketosteroid Excretion During Labor and the Puerperium, p. 629.

Cekon and Ehrlich: Contribution to Question of Corpus Luteum Hormone and 17-Ketosteroid Excretion During Labor and Puerperium, p. 629.

The authors studied 25 patients chosen at random from the obstetrical service of their hospital. The majority of these women were shown to have a progesterone excretion varying between 3 and 10 mg. on the day of delivery, while the postpartum drop gradually reached values below 0.5 mg. on the seventh day. The 17-ketosteroid excretion was elevated from 30 to 77.5 per cent over the previously established normal value of 9 mg. per 24 hours. It was demonstrable that the increased 17-ketosteroid excretion bore no relationship to the level of progesterone excretion and was not related to the sex of the child. The significant increased excretion of 17-ketosteroid immediately post partum described by other workers was not substantiated in the study. The authors postulate that birth is a physiological process and does not produce the acute stress syndrome of Selye. In the authors' series, the only patients who showed a striking acute increase in the 17-ketosteroid excretion were those delivered by surgical procedures in whom nonspecific operative stress was undoubtedly present.

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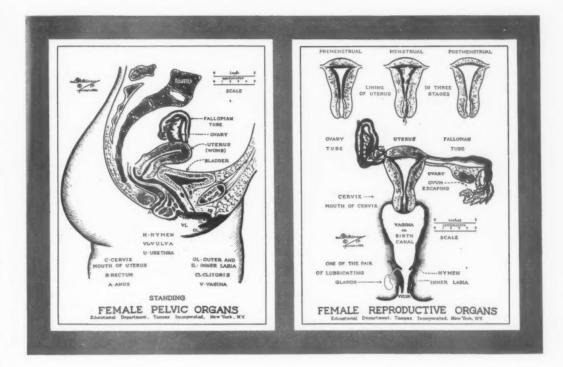
#### ACTA ENDOCRINOLOGICA

The Official Journal of the Endocrinological Societies in Denmark, Finland, Germany, Holland, Norway, Sweden and Switzerland

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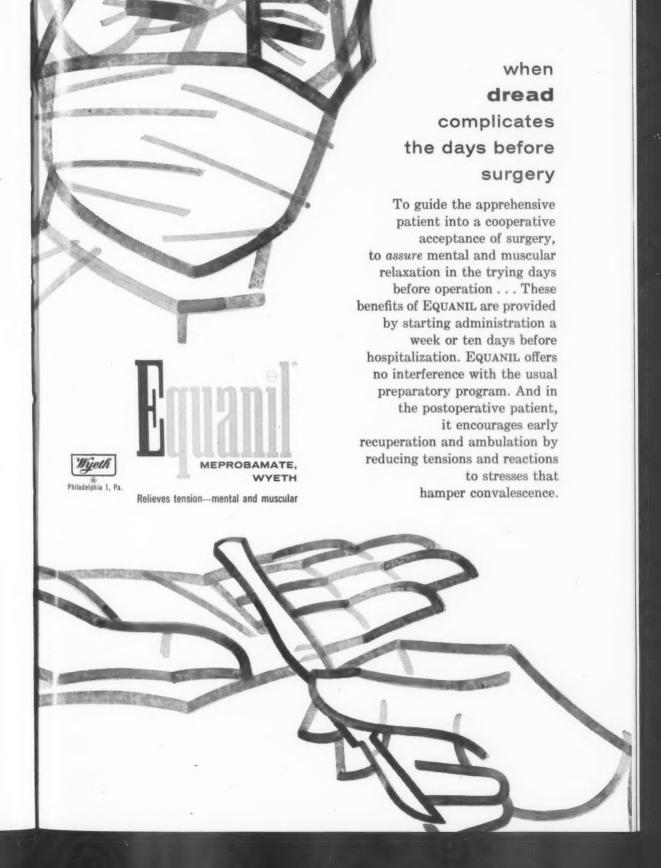
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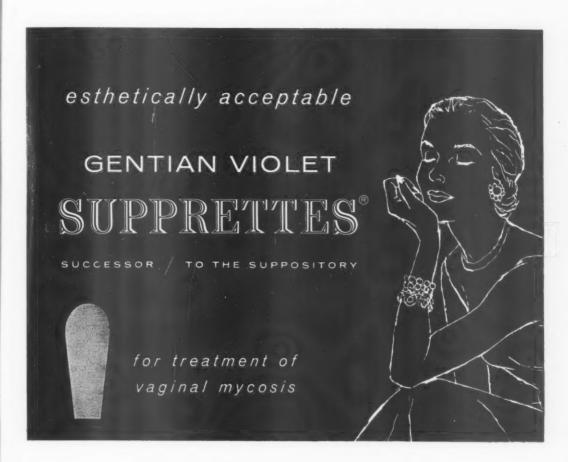


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